Chapter 16

Histamine, Serotonin, & the Ergot Alkaloids

自泌素(Autacoid)

- 自泌素(autacoids)由體內自行分泌，藉由組織液以擴散方式運送至附近組織細胞附近，故又稱為局部激素(local hormones)
- 功能
  - 具有生理作用，如局部血液循環的調節、發炎的形成和過敏反應等；當分泌不正常時則產生病理現象

分類

結構	example
胺類	**Histamine**, **Serotonin**
polypeptide	Angiotensin, endorphin , kinins
不飽和脂肪酸	**Prostaglandin**, Leukotriene, Thromboxane

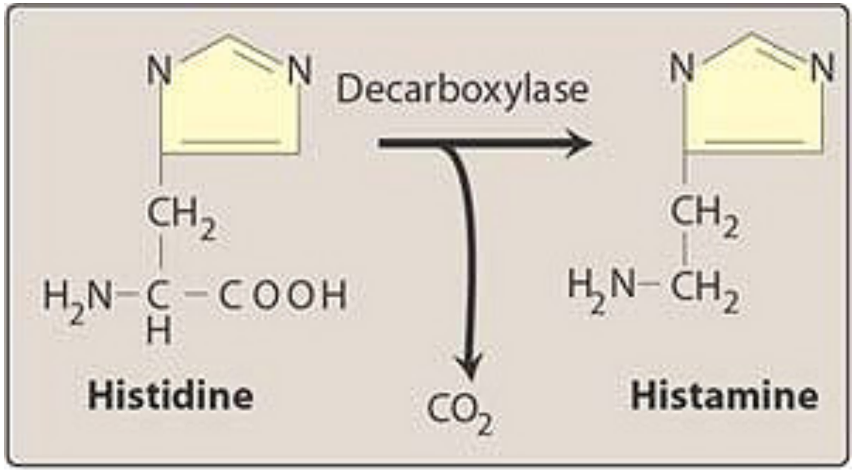
Histamine

- Early hypotheses
  - i.v.⇨ histamine ⇨過敏性休克, tissue injury
  - possible physiologic roles of tissue histamine
- Histamine is formed from the amino acid histidine is stored
  - in mast cells
  - enterochromaffin cells(腸嗜鉻性細胞) in the gut
  - some neurons,
  - other cell types

- Roles
  - allergic (such as urticaria) and inflammatory reactions
  - gastric acid secretion
  - neurotransmitter and neuromodulator
  - Newer evidence indicates that histamine also plays a role in chemotaxis of white blood cells (白血球趨化).

Chemistry & Pharmacokinetics

- Histamine occurs
  - in plants
  - in animal tissues



Certain neoplasms (白血病, 蕁麻疹…)

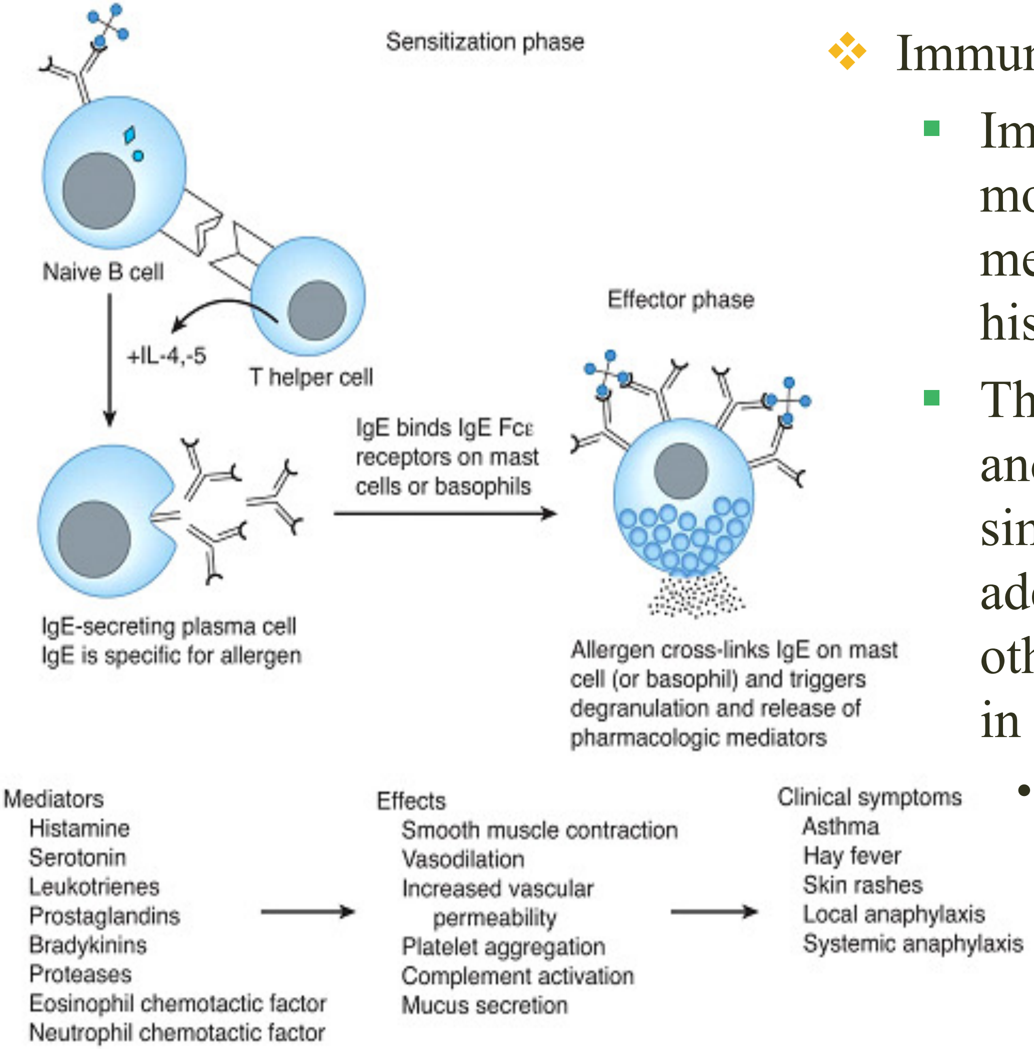
→ **<u>mast cells</u>** or 嗜鹼性白血球⬆

→ excretion of histamine ⬆.

Mast cells在潛在的組織損傷尤其豐富—
nose, mouth, and feet; internal body surfaces; and blood vessels, particularly at pressure points and bifurcations.

- **Non-mast cell** histamine is found in several tissues, including the brain, where it functions as a neurotransmitter.
  - 具有以下作用
    - 心血管調節
    - 熱和體重調節
    - 睡眠與覺醒的腦功能

Storage & Release of Histamine



- Immunologic Release
  - Immunologic processes account for the most important pathophysiologic mechanism of mast cell and basophil histamine release.
  - This type of release also requires energy and calcium. Degranulation leads to the simultaneous release of histamine, adenosine triphosphate (ATP), and other mediators that are stored together in the granules.
    - Histamine released by this mechanism is a mediator **in immediate (type I) allergic reactions**, such as hay fever and acute urticaria.

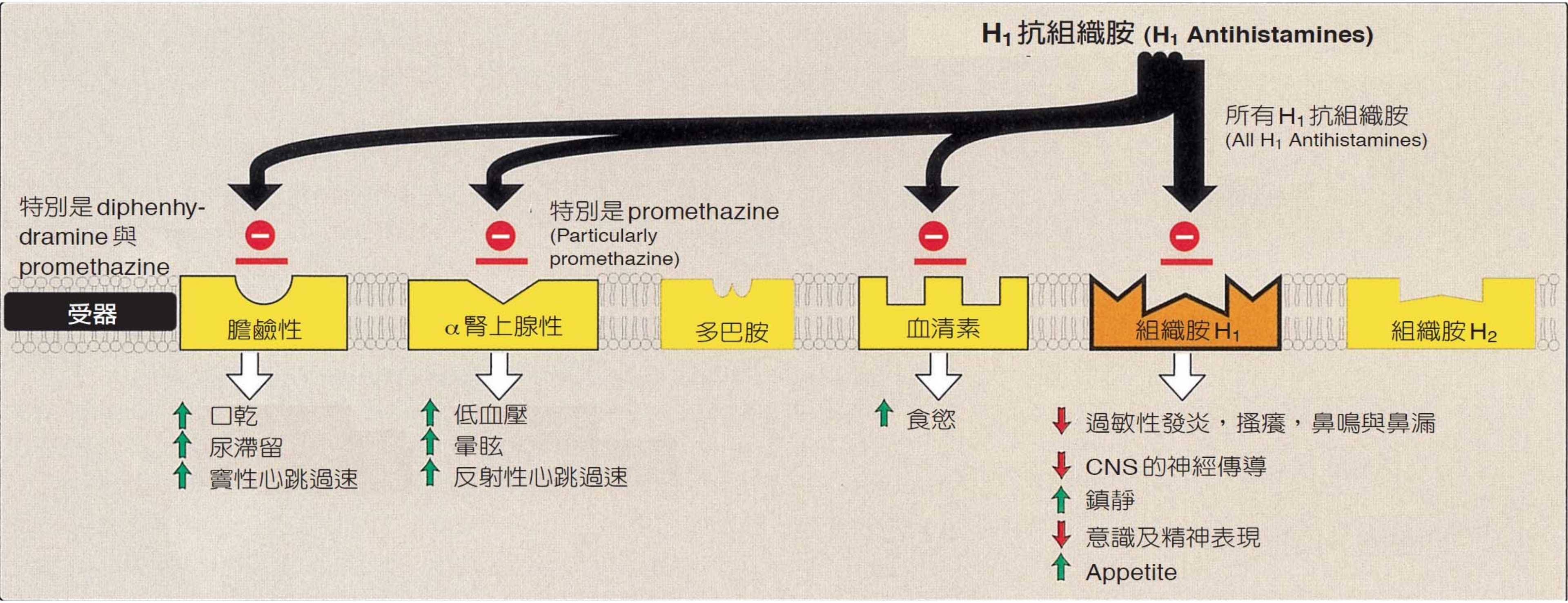
Mechanism of Action

Histamine Receptor Subtypes

Receptor Subtype	Distribution	Postreceptor Mechanisms	Prototypic Antagonist
H_1	Smooth muscle	G_q; ↑IP_3, DAG	Diphenhydramine
H_2	Stomach, heart, mast cells	G_s; ↑cAMP	Cimetidine
H_3	Nerve endings, CNS	G_i; ↓ cAMP	Clobenpropit
H_4	Leukocytes	G_i; ↓ cAMP	—

H_1 Receptor

- Allergic reactions
  - This receptor is important in smooth muscle effects, especially those caused by IgE-mediated responses.
  - Typical responses include
    - 皮膚的疼痛和瘙癢
    - 支氣管收縮
    - 血管擴張



H1 抗組織胺 (H1 Antihistamines)
所有H1 抗組織胺
(All H1 Antihistamines)
特別是diphenhy-
dramine與
promethazine
特別是promethazine
(Particularly
promethazine)
受器
膽鹼性
α腎上腺性
多巴胺
血清素
組織胺H1
組織胺H2
口乾
尿滯留
竇性心跳過速
低血壓
暈眩
反射性心跳過速
食慾
過敏性發炎，搔癢，鼻鳴與鼻漏
CNS的神經傳導
鎮靜
意識及精神表現
Appetite

- H_2 Receptor
  - This receptor mediates gastric acid secretion by parietal cells in the stomach
  - has a cardiac stimulant effect
  - A third action is to reduce histamine release from mast cells
    - a negative feedback effect
    - activation of adenylyl cyclase →cAMP ⬆

- H_3 Receptor
  - This receptor appears to be involved mainly in **presynaptic modulation of histaminergic neurotransmission** in the central nervous system (CNS).
    - Food intake and body weight increase in H_3-receptor knockout animals.
  - In the periphery
    - it appears to be a presynaptic heteroreceptor with modulatory effects on the release of other transmitters
- H_4 Receptor
  - The H_4 receptor is located on leukocytes (especially eosinophils) and mast cells and is involved in chemotactic responses by these cells. Like H3, it is Gi coupled.

Tissue and Organ System Effects of Histamine

1. Nervous System
2. Cardiovascular System
3. Bronchiolar Smooth Muscle
4. Gastrointestinal Tract Smooth Muscle
5. Other Smooth Muscle Organs
6. Secretory Tissue
7. Metabolic Effects

1. Nervous System

- Histamine is a powerful stimulant of sensory nerve endings
  - especially those mediating pain and itching.
- This H_1-mediated effect is an important component of the presynaptic H_3 receptors play important roles in modulating release of several transmitters in the nervous system.
  - H_3 agonists → acetylcholine ⬇ amine ⬇ peptide ⬇ (in various areas of the brain and in peripheral nerves)

2. Cardiovascular System

- In humans→ i.v. histamine → systolic and diastolic blood pressure ⬇, heart rate⬆
  - Mechanism
    - direct vasodilator → blood pressure ⬇ → heart rate ⬆(reflex tachycardia)
- Small doses of histamine → H_1-receptor activation → Vasodilation
- Higher doses of histamine → H_2-receptor activation → direct cardiac stimulation
- In humans
  - the cardiovascular effects of small doses of histamine can usually be antagonized by H_1-receptor antagonists alone.

3. Bronchiolar Smooth Muscle

- In guinea pigs→ histamine → H_1 receptors → bronchoconstriction
- In humans → histamine (small doses)→ normal airways → not marked
  - Such individuals (bronchial hyperreactivity) may be 100 to 1000 times more sensitive to histamine than are normal subjects

4. Gastrointestinal Tract Smooth Muscle

- Histamine →contraction of intestinal smooth muscle
- large doses of histamine → H_1 receptors →diarrhea

5. Secretory Tissue

- Histamine →H_2-receptor → cAMP⬆ → gastric acid secretion

6. The "Triple Response"

- At the site of injection
  - 皮膚變紅(dilation of small vessels)
  - edematous wheal (丘疹)
  - 不規則發紅(flare)圍繞丘疹
    - The is said to be caused by an axon reflex. A sensation of itching may accompany these effects.

Wheal & flare (丘疹及潮紅)

Clinical Pharmacology of Histamine

- Clinical Uses
  - Histamine has no other current clinical applications.
- Toxicity & Contraindications
- Adverse effects of histamine release, like those following administration of histamine, are dose-related
  - Flushing
  - Hypotension
  - Tachycardia
  - Headache
  - wheals
  - Bronchoconstriction
  - gastrointestinal upset are noted

Histamine receptor

	H_1 receptor	H_2 receptor	H_3 receptor
分布位置	肺、皮膚、肥大細胞	胃黏膜	分佈在突觸前、腦部
生理功能	❖支氣管收縮 ❖微血管通透性增加 ❖與癢、發炎、過敏有關 ❖中樞神經傳遞物質引起嘔吐、暈眩等	❖與胃酸分泌有關 ❖心跳加、快心收縮力增強	❖調節Histamine的釋出 ❖作用尚未明瞭

- 組織胺製劑
  - Betazole用於診斷胃功能
- 抗組織胺製劑
  - Anti-H1
    - First generation
      - Diphenhydramine (Benadryl®)
      - Chlorpheniramine
      - Cyproheptadine (Periactin®)
      - Azatadine
      - Phenindamine (Theophorin®)
      - Cyclizine (Marezine®)
      - Meclizine (Bonamine®)
      - Promethazine
    - Second generation
      - Astemizole (Hismanal®)
      - Terfenadine (Teldane®)
      - Fexofenadine (Allegra®)
      - Loratadine
      - Acrivastine
      - Cetirizine (Zyrtec®)
      - mequitazine

- Anti-H2
  - Cimetidine(Tagamet®)
  - Ranitidine(Zantac®)
  - Famotidine(Gaster®)
  - Nizatidine(Tazac®)

H_1-Receptor Antagonists

- used in the treatment of allergic conditions
  - "cold pills" and sleep aids

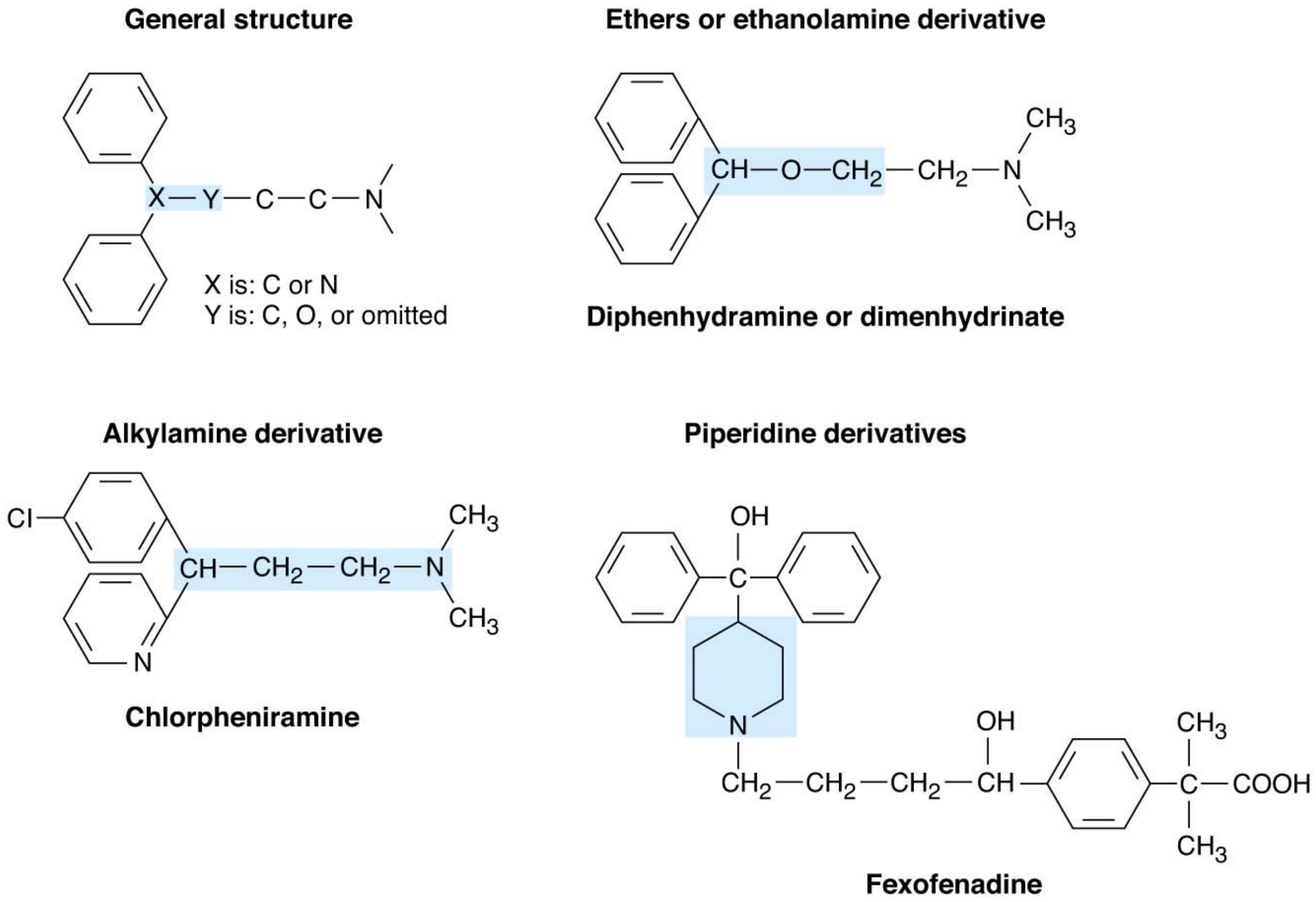
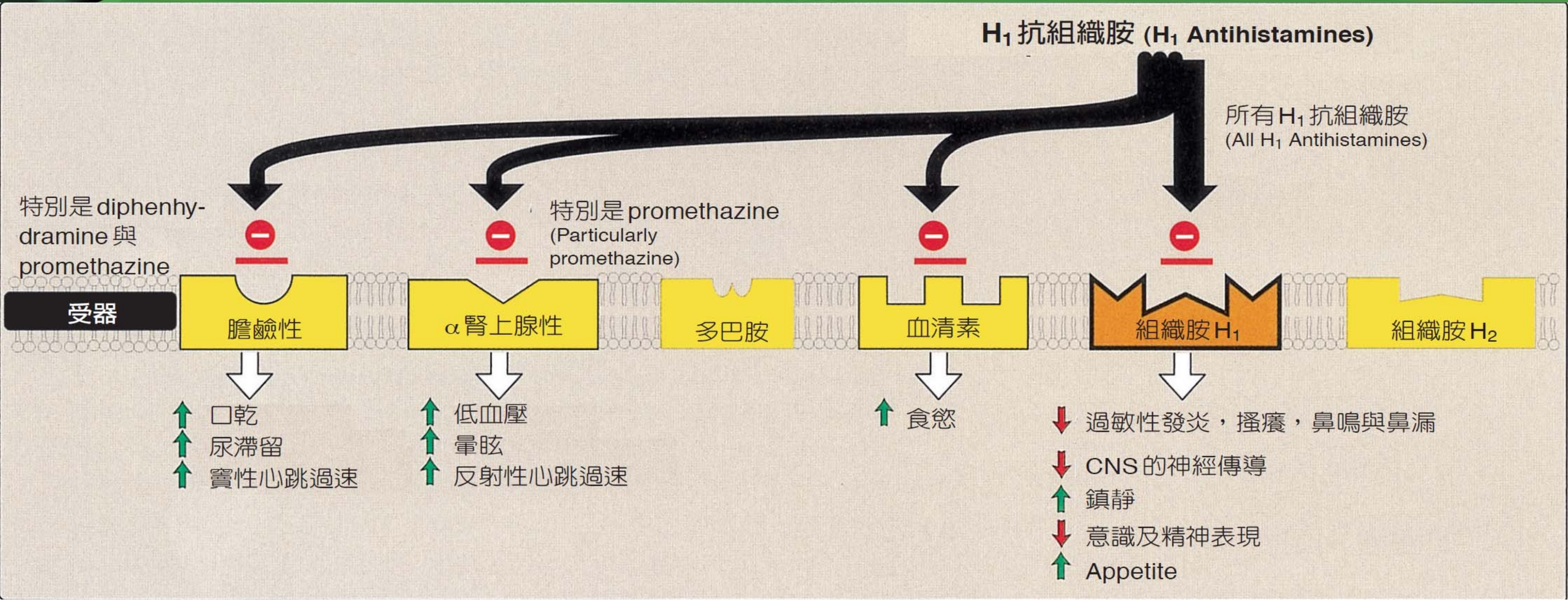


FIGURE 16–1 General structure of H_1-antagonist drugs and examples of the major subgroups. Chemical subgroups are indicated by shading.

Drugs	Dose	Anti-Ach	Comments
FIRST-GENERATION ANTIHISTAMINES			
Carbinoxamine	4–8 mg	+++	Slight to moderate sedation
Diphenhydramine	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Hydroxyzine	15–100 mg	nd	Marked sedation
Cyclizine	25–50 mg	–	Slight sedation; anti-motion sickness activity
Meclizine	25–50 mg	–	Slight sedation; anti-motion sickness activity
Brompheniramine	4–8 mg	+	Slight sedation
Chlorpheniramine	4–8 mg	+	Slight sedation; common component of OTC "cold" medication
Promethazine	10–25 mg	+++	Marked sedation; antiemetic; α block
Cyproheptadine	4 mg	+	Moderate sedation; also has antiserotonin activity

Drugs	Dose	Anti-Ach	Comments
SECOND-GENERATION ANTIHISTAMINES			
Fexofenadine (Allegra)	60 mg	–	
Loratadine (Claritin)	10 mg	–	Longer action
Cetirizine (Zyrtec)	5–10 mg	–	
mequitazine	5 mg		

Pharmacodynamics H_1-Receptor Antagonists



Adrenoceptor-Blocking Actions

Sedation
Antinausea and Antiemetic Actions

Antiparkinsonism Effects

Serotonin-Blocking Action

Local Anesthesia：block sodium channels , potassium channels
OtherActions： inhibit mast cell release of histamine and some other mediators of inflammation

Clinical Pharmacology of H_1-Receptor Antagonists

- Clinical Uses
  - First-generation H1-receptor blockes are among the most extensively promoted and used over-the-counter drugs.
    - 1th H1-receptor blockers → sedation
    - 2th H1-receptor blockers → weak sedation or nonsedation

1. Allergic Reactions
2. Motion Sickness and Vestibular(前庭) Disturbances
3. Nausea and Vomiting of Pregnancy

First-generation H_1-receptor blockers

- Diphenhydramine
  - 作用
    - 注射治療過敏最佳藥物，強力抑制 CNS，運動困難、另可止吐、止癢。
    - 高血壓及心臟病者須慎用，局部使用易過敏。
    - 與 chlortheophylline 形成之鹽→ (dimenhydrinate; Dramamine)，用於暈車及孕婦止吐。
  - 副作用
    - 嗜眠。

- Cyproheptadine
  - 作用
    - 兼具抗 **$5\text{-}HT_2$**，用於止癢。
  - 副作用
    - 鎮靜，停藥後 3～4 天即可消除。

- Azatadine(Zadine)
  - 作用
    - 強效且長效，亦具抗 5-HT，類似 cyproheptadine

- Meclizine
  - 作用
    - 強力抗過敏，起效遲，藥效久（9～24 小時），預防暈車及眩暈。
  - 副作用
    - 嗜眠及阻抑副交感神經。
  - 注意
    - 孕婦、青光眼及無尿患者禁用。
- Cyclizine
  - 作用
    - 預防暈車、暈船及治療術後噁心、嘔吐，而不作抗組織胺用。
  - 副作用
    - 嗜眠及抗膽鹼。

- Promethazine
  - 作用
    - 極強效及長效 phenothiazine 類抗組織胺，廣用於枯草熱、蕁麻疹、暈車船及術後噁心、嘔吐，但不外用局部，以免過敏。
    - 臨睡前服用，藥效維持到第二天全天，然鎮靜嗜眠副作用在第二天清晨即已消退。
    - 有時與 pethidine、chlorpromazine 合併注射，作為麻醉前給藥。對治療帕金森氏病也有效。
  - 副作用
    - 口乾、視覺渾濁，有時嗜眠。
  - 注意
    - 避免與酒併服。

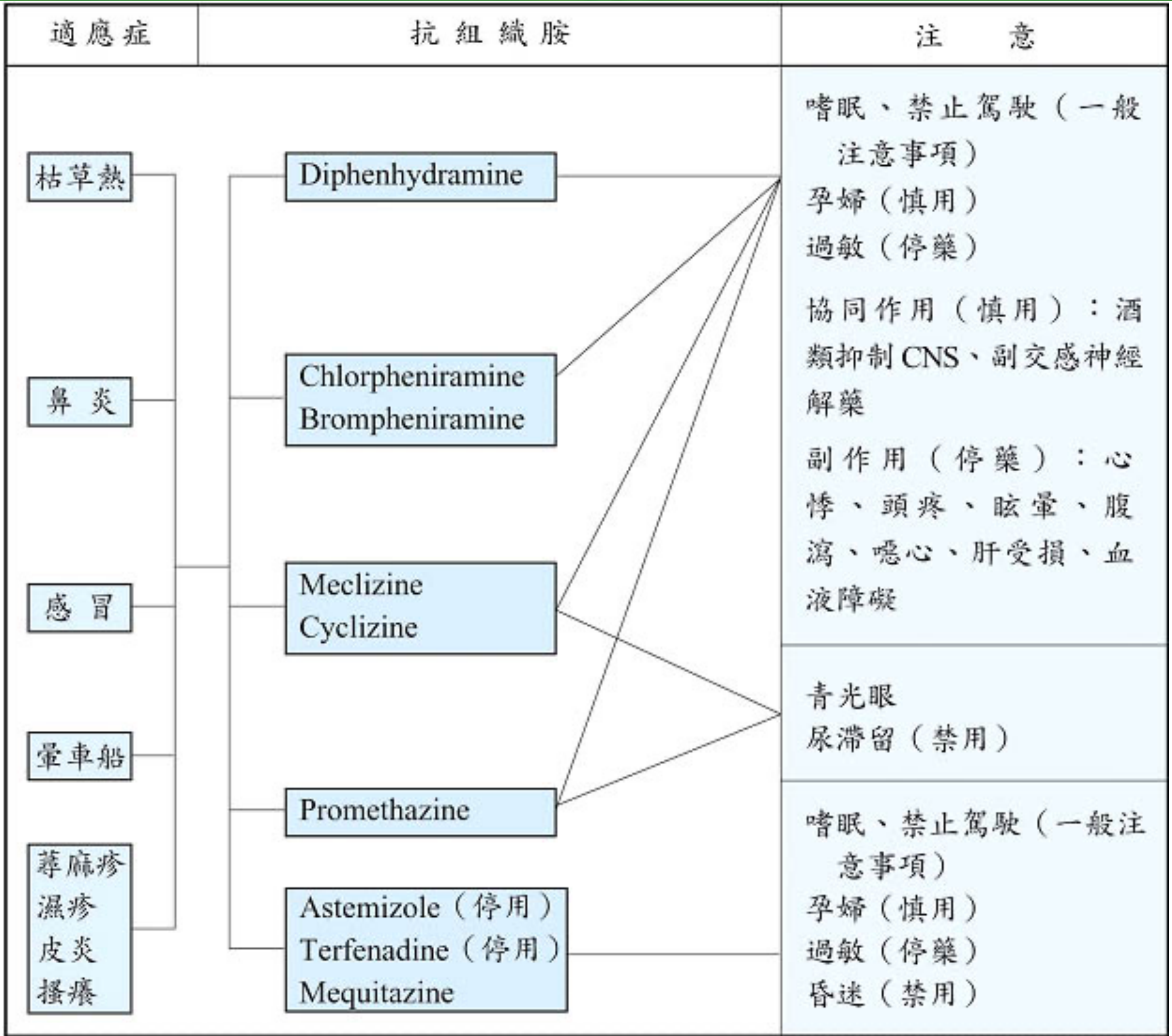
Second-generation H1-receptor blockers

- Fexofenadine (Allegra®)
  - 作用
    - 為 terfenadine 活性代謝物，作用亦類似，但本藥不經代謝即有藥效，因之無心毒性。
    - 吸收不受食物影響，多以原態經糞便及尿排泄，適於肝功能不全病人，但腎功能不良者需減量。
  - 副作用
    - 噁心、疲倦、消化不良、病毒感染、經痛。

- Loratadine
  - 作用
    - 由第一代藥 azatadine 及 cyproheptadine 修飾結構而得，已無 CNS 副作用。
    - 藥效極佳，另有抗 5-HT 作用。
- Acrivastine
  - 作用
    - 結構、藥效、作用時限均類似 triprolidine，但抗 ACh 及嗜眠副作用低。
    - 與去鼻充血劑 pseudoephedrine 口服併用。

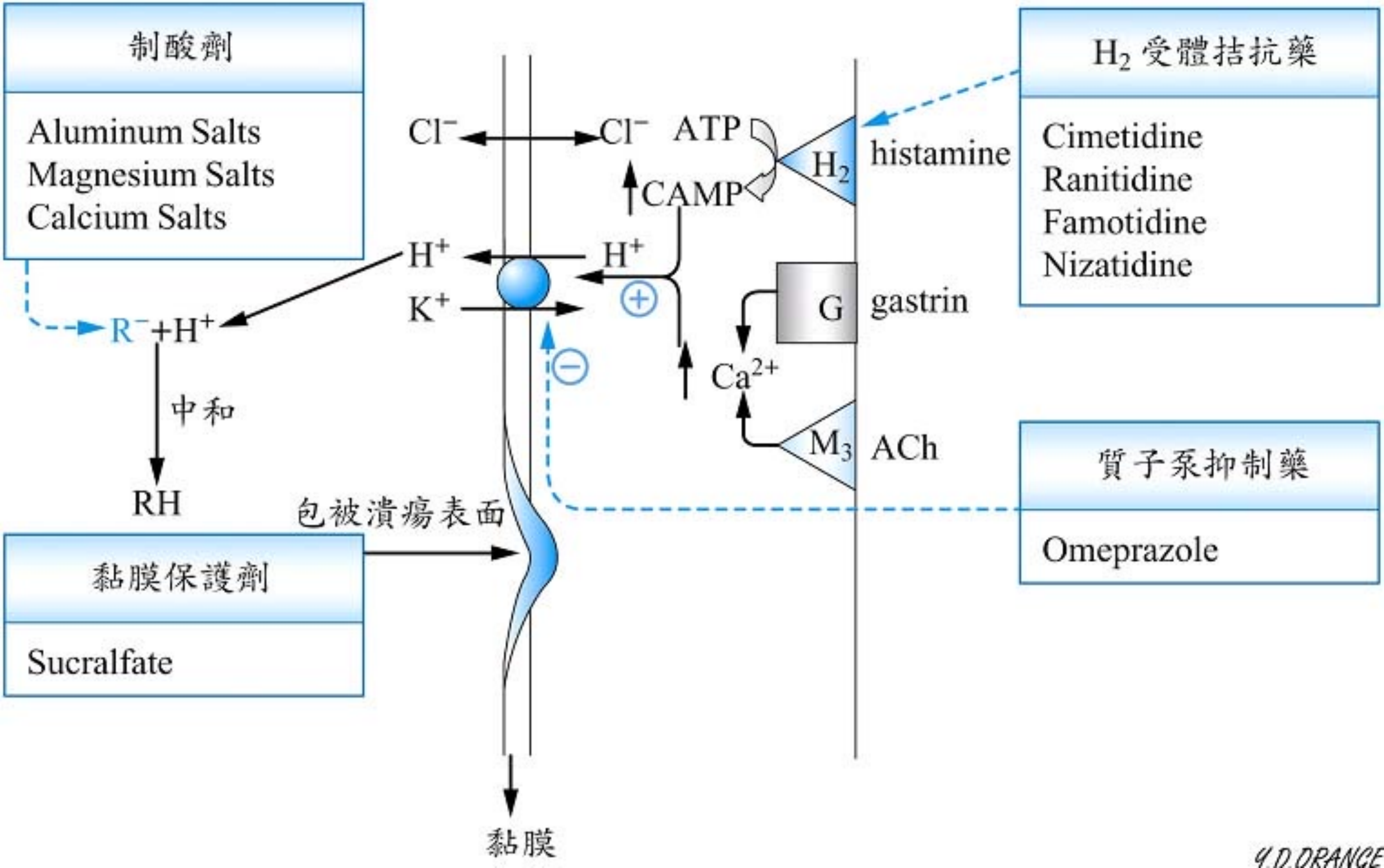
- Cetirizine (Zyrtec®)
  - 作用
    - 為第一代藥 hydroxyzine 代謝物，但不穿透 BBB。
    - 優點為作用快速，每日只需服用一次，無心毒性、無 CNS 毒性。
  - 副作用
    - 嗜眠、倦怠、口乾、眩暈。
  - 注意
    - 駕駛或機械操作者需慎用
- Mequitazine (Primalan®)
  - 作用
    - 屬於 phenothiazine 類，不通過 BBB，不引起鎮靜，藥效很長（24 小時）。
    - 口服 6 小時後達最高血中濃度，輕微抑制副交感神經。在 10 mg 劑量時產生輕微鎮靜嗜眠，因此治療範圍狹窄

Anti-histamine



H_2-Receptor Antagonists

- The development of H_2-receptor antagonists
  - was based on the observation that H_1 antagonists had no effect on histamine-induced acid secretion in the stomach.
  - Cimetidine, Ranitidine and other H2 antagonists
    - must be used cautiously in patients with hepatic impairment and adjust dosage in patient with renal impairment.
  - Inhibition of hepatic metabolism of warfarin, diazepam, propranolol, theophylline, and other drugs metabolized by hepatic mixed-function oxidase system



制酸劑
Aluminum Salts
Magnesium Salts
Calcium Salts
H₂ 受體拮抗藥
Cimetidine
Ranitidine
Famotidine
Nizatidine
質子泵抑制藥
Omeprazole
黏膜保護劑
Sucralfate
Cl⁻
Cl⁻
ATP
CAMP
H⁺
H⁺
K⁺
R⁻+H⁺
中和
RH
包被潰瘍表面
黏膜
H₂
histamine
G
gastrin
Ca²⁺
M₃
ACh
Y.D.DRANCE

H2受體拮抗劑

- Cimetidine (Tagamet®), Ranitidine (Zantac®)
  - 作用
    - 藥效相當，口服或注射，以 Ranitidine 之副作用較少，療效極佳 (70～90%)，藥效長達七小時，為治療首選藥
    - Ranitidine 較 cimetidine 長效，服藥次數較少，不抑制肝代謝的酵素，因而沒有藥物相互作用。本藥無抗雄性激素效應，不造成男性女乳或陽痿
    - Cimetidine 抑制肝 cytochrome P450 氧化酵素系統，造成嚴重的藥物相互作用
    - Cimetidine 的適應症包括：
      - 短期治療十二指腸潰瘍
      - 預防十二指腸潰瘍復發
      - 治療過度分泌，例如 Zöllinger-Ellison 症候群
  - 副作用
    - Cimetidine 短期用藥幾無副作用；長期（一年）可致男子女乳症 (gynecomastia)、陽痿，停藥後可恢復正常

- Famotidine (Gaster®)
  - 作用
    - 口服或 IV 效果極佳，藥效更強久，並增進胃粘膜的防禦力，劑量僅需每天二次，每次 20 mg。副作用更少，是最佳 H2 拮抗劑
- Nizatidine (Tazac®)
  - 作用
    - 口服生體可用率極佳 (>90%)，無抗雄性激素效應或抑制 cytochrome P450 氧化酵素

項　　目	Cimetidine	Ranitidine	Famotidine
初劑量	400 mg × 2 或 200 mg × 3 + 400 mg	150 mg × 2	20 mg × 2
最大劑量	400 mg × 3	300 mg × 3	
維持量	睡前 400 mg	睡前 150 mg	
相對抑酸活性	1	12	72.6
口服半生期（小時）	2.2	2～2.5	3.3
十二指腸潰瘍治癒率 (%)	45～84（四週） 92～95（八週）	63～78（四週） 85～92（八週）	
高血泌乳素	+	−	−
抗雄性素效應	+	−	−
抑制藥物肝代謝	+	−	−
副作用發生率 (%)	3.7	3.8	2.5

Clinically important Drug interactions with Cimetidine

Drug	Mechanism	Clinical significance
Tricyclic Antidepressants	Clearence ↓	↑ Side effect
Benzodiazepines	Clearence ↓	↑ sedation
Phenytoin	Clearence ↓	↑ Toxicity
Ketoconazole	Absorption ↓	↓ Effect
Metronidazole	Clearence ↓	Unknown
Lidocaine	Clearence ↓	↑ Toxicity
Quinidine	Clearence ↓ (Hepatic & renal)	Prolonged QT interval
Labetalol	Unclear	↓ Blood pressure
Propranolol	Clearence ↓	hypotension, bradycardia
Nifedipine	↑ AUC 60%	↑ Effect
Verapamil	Clearence ↓ 21% ↓ metabolism	No dynamic effects reported
Theophylline	Clearence ↓	↑ Toxicity
Warfarin	Clearence ↓	↑ Prothrombin time

治療

- 必須使用抗生素來去除幽門螺旋菌
  - amoxicillin、 tetracycline、metronidazole …
- 二合一療法
  - 一種抗生素加上一種輔助藥物 (Tagamet 、 Zantac 、 Losec…)
- 三合一療法
  - 二種抗生素加上一種輔助藥物
- 四合一療法
  - 二種抗生素加上二種輔助藥物

2週療程

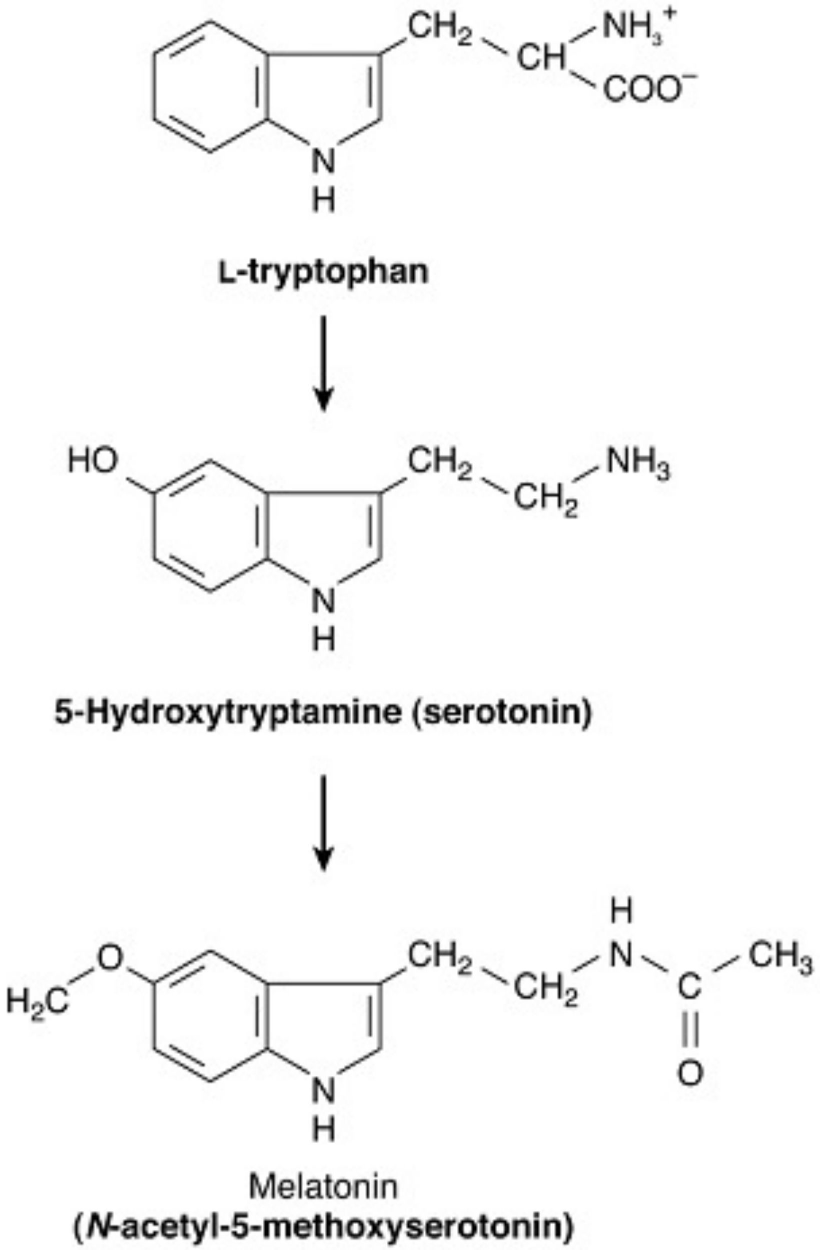
Used for H. pylori & Ulcers					
Drug 1	Drug 2	Drug 3	Drug 4	Duration	Efficacy
Bismuth 2 tab. QID	Metronidazole 250 mg TID/QID	Tetracycline * 500mg QID	Omeprazole 20 mg BID	1-2 weeks	94-98%
Bismuth 2 tab. QID	Metronidazole 250 mg TID/QID	Amoxicillin 500mg TID/QID		1 week 2 weeks	75-81% 80-94%
Bismuth 2 tab. QID	Clarithromycin 500mg TID	Tetracycline * 500mg QID		1-2 weeks	> 90%
Bismuth 2 tab. QID	Clarithromycin 500mg TID	Amoxicillin 500mg QID		1-2 weeks	> 90%
Bismuth 2 tab. QID	Clarithromycin 500mg BID	Omeprazole 20 mg BID		8 days	80 %
Metronidazole 500 mg BID	Omeprazole 20 mg BID	Clarithromycin 250mg BID		1-2 weeks	85-91 %
Amoxicillin 1 gm BID	Omeprazole 20 mg BID	Clarithromycin 500mg BID		1-2 weeks	80-95 %
Amoxicillin 1 gm BID	Omeprazole 20 mg BID	Metronidazole 500 mg BID		1-2 weeks	77-86 %
Amoxicillin 500mg TID	Omeprazole 40 mg daily			2 weeks	54-79 %
Amoxicillin 500mg QID	Clarithromycin 500mg TID			2 weeks	> 90 %
Amoxicillin 700mg TID	Metronidazole 500 mg TID			2 weeks	> 85%
Clarithromycin 500mg TID	Omeprazole 40 mg daily			2 weeks	83%
Clarithromycin 500mg TID	Ranitidine 150 mg BID			2 weeks	82-94%

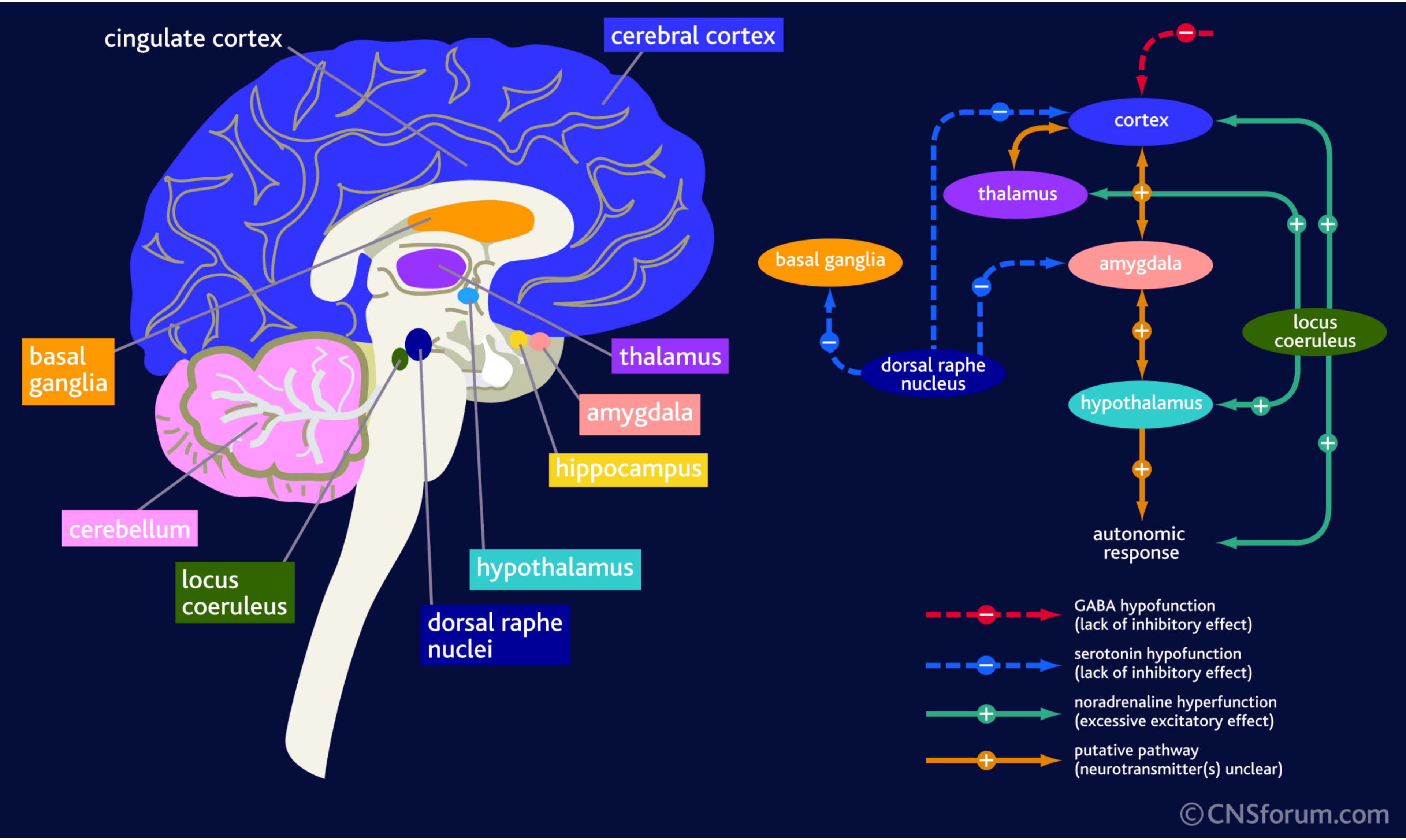
H_3 & H_4-Receptor Antagonists

- Although no selective H_3 or H_4 ligands are presently available for general clinical use, there is great interest in their therapeutic potential.
  - H_3-selective ligands may be of value in sleep disorders, obesity, and cognitive and psychiatric disorders.
    - Tiprolisant, an inverse H_3-receptor agonist, has been shown to reduce sleep cycles in mutant mice and in humans with narcolepsy.
    - Increased obesity has been demonstrated in both H_1- and H_3-receptor knockout mice.
  - H_4 blockers have potential in chronic inflammatory conditions such as asthma, in which eosinophils and mast cells play a prominent role.
    - Several studies have suggested that H_4-receptor antagonists may be useful in pruritus (搔癢).

Serotonin (5-Hydroxytryptamine)

- Serotonin is an important neurotransmitter, a local hormone in the gut, a component of the platelet clotting process, and is thought to play a role in migraine headache
  - over 90% of the serotonin in the body is found in enterochromaffin cells in the gastrointestinal tract
  - serotonin is also found in platelets ,in the raphe nuclei of the brain stem
  - A few foods contain





cingulate cortex
cerebral cortex
basal ganglia
thalamus
amygdala
hippocampus
cerebellum
locus coeruleus
hypothalamus
dorsal raphe nuclei
cortex
thalamus
basal ganglia
amygdala
locus coeruleus
dorsal raphe nucleus
hypothalamus
autonomic response
GABA hypofunction (lack of inhibitory effect)
serotonin hypofunction (lack of inhibitory effect)
noradrenaline hyperfunction (excessive excitatory effect)
putative pathway (neurotransmitter(s) unclear)
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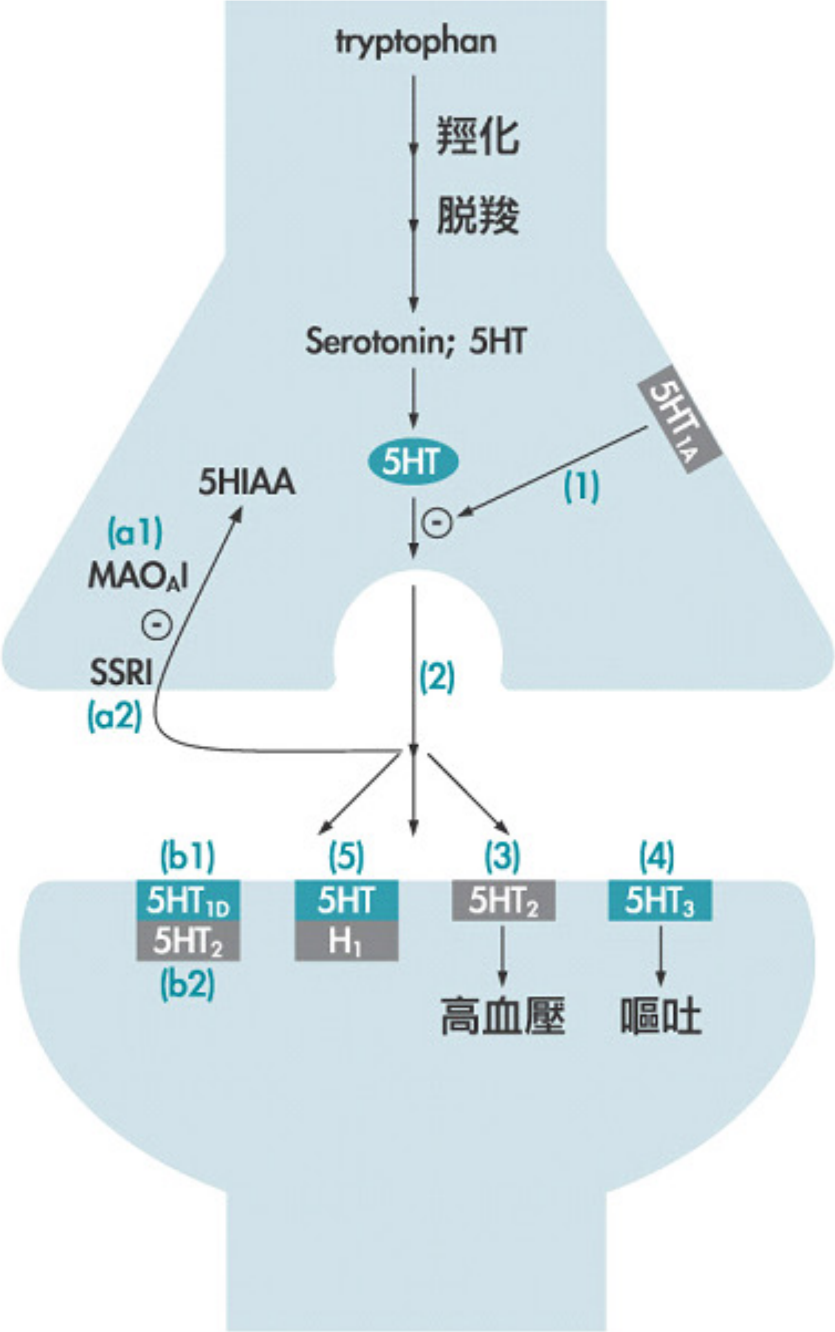
Mechanisms of Action

Receptor Subtype	Distribution Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus; G_i, cAMP	8-OH-DPAT	WAY100635
5-HT_{1B}		Sumatriptan, CP93129	
5-HT_{1D}	Brain; G_i, cAMP	Sumatriptan	
5-HT_{1E}			
5-HT_{1F}		LY334370	
5-HT_{1P}	Enteric nervous system; G_o, slow EPSP	5-Hydroxyindalpine	Renzapride
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex; G_q, IP_3	α-Methyl-5-HT	Ketanserin
5-HT_{2B}	Stomach fundus; G_q, IP_3	α -Methyl-5-HT	SB204741
5-HT_{2C}	Choroid, hippocampus, substantia nigra; G_q, IP_3	α -Methyl-5-HT	Mesulergine
5-HT_3	Area postrema, sensory and enteric nerves Receptor is a Na^+-K^+ ion channel	2-Methyl-5-HT, m-chlorophenylbiguanide	Granisetron, ondansetron, tropisetron
5-HT_4	CNS and myenteric neurons, smooth muscle; G_s, cAMP	5-Methoxytryptamine, renzapride, metoclopramide	
5-$HT_{5A,B}$	Brain, cAMP		
5-$HT_{6,7}$	Brain, G_s, cAMP		Clozapine (5-HT_7)



增加5HT在突觸間隙及受體致效劑

A. 抗憂鬱藥

(a1) 減少被分解MAO_AI，Moclobemide

(a2) 抑制再回收SSRI，Fluoxetine

B. 預防及治療偏頭痛

(b1) $5HT_{1D}$受體致效劑，Sumatriptan

(b2) $5HT_2$部份致效劑，Methysergide

降低5HT在突觸間隙間及拮抗劑

(1) $5HT_{1A}$部份致效劑(迴饋抑制5HT釋出)，Buspirone(抗焦慮)

(2) 排空5HT致被分解，Resepine(降血壓)

(3) $5HT_2$受體拮抗劑，Ketanserin. Ritanserin(降血壓)

(4) $5HT_3$受體拮抗劑，Ondansetron(止吐)

(5) 5HT及H_1拮抗劑，Cyproheptadine(抗過敏)

Tissue and Organ System Effects Serotonin

- Nervous System
  - $5\text{-}HT_3$ receptors in the gastrointestinal tract and in the vomiting center of the medulla participate in the vomiting reflex (**chemoreceptor reflex**).
    - They are particularly important in vomiting caused by chemical triggers such as cancer chemotherapy drugs.
      - 5-HT3 antagonist
        - » Ondansetron (zofran®)
  - $5\text{-}HT_{1P}$ and $5\text{-}HT_4$ receptors also play important roles in enteric nervous system function
  - **Melatonin**
    - Activation of the MT_1 receptor results in sleepiness, whereas the MT_2 receptor may be related to the light-dark synchronization of the biologic circadian clock
    - **Ramelteon** is a selective MT_1 and MT_2 agonist that is approved for the medical treatment of insomnia.

- 副作用
  - 頭痛、感覺燥熱與潮紅、便秘；若是注射劑，靜脈注射部位出現局部反應
- 注意事項
  - 對於中度或重度肝功能損害者，對於這類患者每日劑量不可超過8mg。

- Cardiovascular System
  - Serotonin→5-HT_2 receptors→contraction of vascular smooth muscle
    - 5-HT_2 antagonist
      - Ketanserin (Sufrexal®)
  - A triphasic blood pressure response (injection of serotonin)
    - heart rate, cardiac output, and blood pressure ⬇
    - pressure increases (vasoconstriction) ⬆
    - blood pressure ⬇ (vasodilation in vessels supplying skeletal muscle)
  - Serotonin causes blood platelets to aggregate by activating **5-HT_2** receptors

- Respiratory System
  - Serotonin has a small direct stimulant effect on bronchiolar smooth muscle in normal humans, probably via $5\text{-}HT_{2A}$ receptors
- Gastrointestinal Tract
  - Serotonin is a powerful stimulant of gastrointestinal smooth muscle, increasing tone and facilitating peristalsis.
    - Serotonin→$5\text{-}HT_2$ smooth muscle receptors, enteric nervous system
- Skeletal Muscle
  - $5\text{-}HT_2$ receptors are present on skeletal muscle membranes, but their physiologic role is not understood.
  - **Serotonin syndrome** (MAO inhibitors, SSRIs…..)

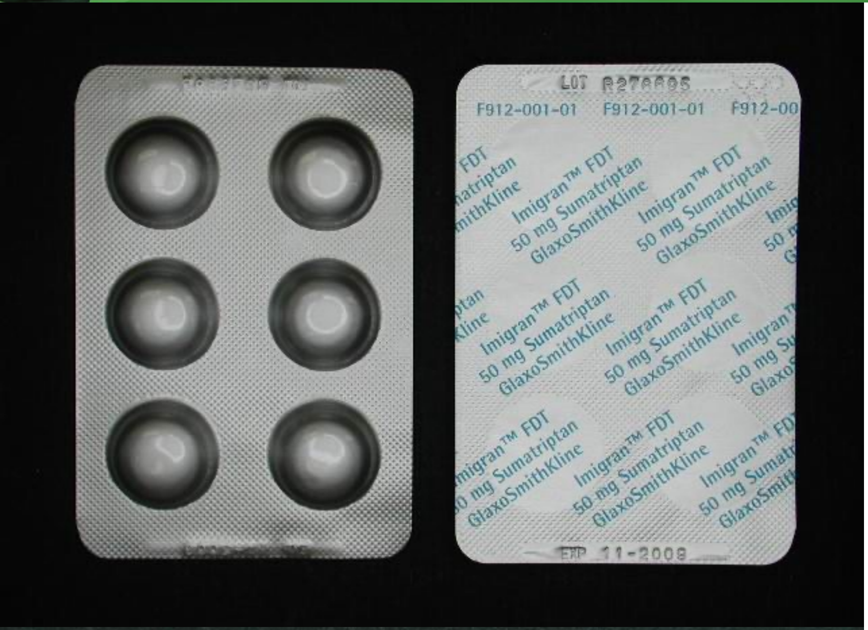
    →skeletal muscle contractions
    - Although the hyperthermia of serotonin syndrome results from excessive muscle contraction, serotonin syndrome is probably caused by a central nervous system effect of these drugs

Characteristics of Serotonin Syndrome and Other Hyperthermic Syndromes

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy
Serotonin syndrome	SSRIs, second generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation and ventilation; consider 5-HT**$_2$ block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Diphenhydramine (parenteral), cooling if temperature is very high, sedation with benzodiazepines**
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene, cooling**

Clinical Pharmacology of Serotonin

- **Buspirone**
  - Mechanism
    - 5-HT_{1A} agonist
  - Clinical Applications
    - Anxiolytics
- **Sumatriptan (triptans), <u>ergot alkaloids</u>**
  - Mechanism (5-$HT_{\mathbf{1D}/1B}$ agonist)
    - may activate 5-HT_{1D}/$_{1B}$ receptors on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides
    - the vasoconstrictor actions of direct 5-HT agonists (the triptans and ergot) may prevent vasodilation and stretching of the pain endings
  - Clinical Applications
    - in the treatment of acute migraine and cluster headache attacks



<u>建議劑量</u>

成人：單次最多服用100 mg；若二小時後症狀未緩解，可再服用第二劑，但每日不可超過300 mg。建議sumatriptan每週不可服用超過兩天。

兒童：Sumatriptan對16歲以下兒童的安全性及有效性尚未確立。

健保限制需符合下列規定，才可依健保給付sumatriptan之治療：

一、 限成人符合國際頭痛協會(InternationalHeadache Society)1988年訂定的「偏頭痛」診斷標準者：

A.至少有五次能符合B至D項的發作。

B.頭痛發作持續四至七十二小時。

C.頭痛至少具下列二項特徵：

1. 單側
2. 搏動性
3. 程度中等或重度(日常生活受限制甚或禁絕)
4. 上下樓梯或類似之日常活動會使頭痛加劇

D.當頭痛發作時至少有下列情形之一：

1. 噁心或嘔吐
2. 畏光及怕吵

二、偏頭痛之發作嚴重影響日常生活(無法工作或作家事)者。

三、經使用其他藥物無效者。

四、每月限使用一次，每次處方不超過100mg。

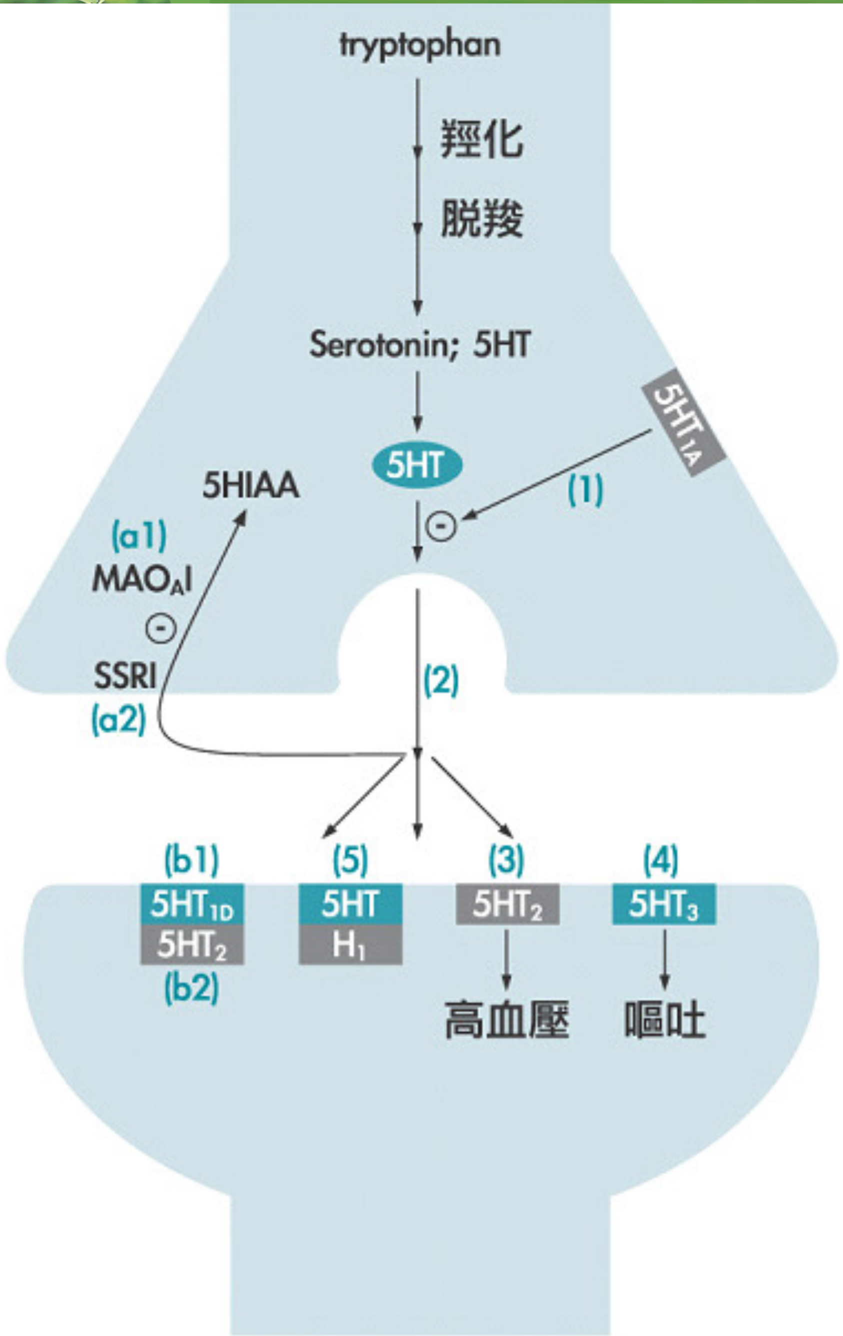
五、不得同時處方含有ergotamine 或其衍生物之製劑。

六、不得作為預防性使用。

七、不得使用於曾患有心肌梗塞、缺血性心臟病、Prinzmetal氏狹心症、冠狀血管痙攣者及高血壓未受控制的患者。

Cisapride

- Mechanism
  - a 5-HT_4 agonist
- Clinical Applications
  - was used in the treatment of gastroesophageal reflux (胃食道逆流) and motility disorders
- Toxicity
  - Arrhythmia
- Drugs
  - **Mosapride**
  - **Tegaserod**
    - irritable bowel syndrome with constipation (激躁性結腸症)



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Serotonin-Receptor Antagonists

- **Cyproheptadine**
  - Mechanism
    - H_1-receptor-blocking as well as 5-HT_2-blocking action
- **Ketanserin**
  - Mechanism
    - blocks 5-HT_2 receptors
    - blocks α_1 adrenoceptors
- **Ritanserin**
  - Mechanism
    - blocks 5-HT_2 receptors
- **Ondansetron**
  - Mechanism
    - 5-HT_3 antagonist
  - Clinical Applications
    - 預防癌症治療〈化學藥物治療或放射線治療〉所引起的噁心嘔吐，或手術後引. 起的噁心嘔吐

The Ergot Alkaloids

Effects of some ergot alkaloids at several receptors

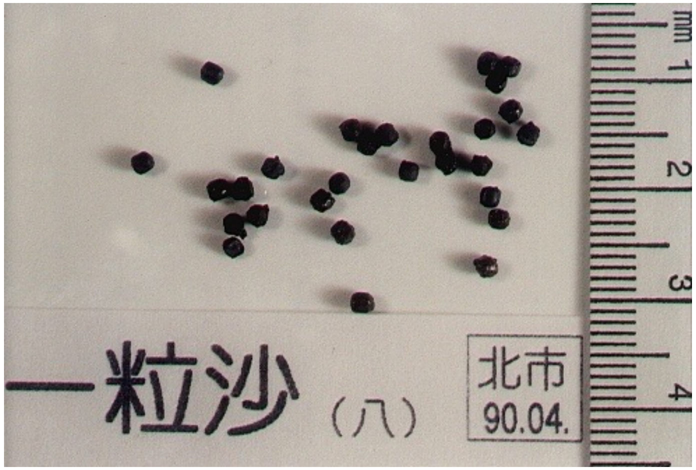
Ergot Alkaloid	Alpha Receptor (α_1)	Dopamine Receptor (D_2)	Serotonin Receptor (5-HT_2)	Uterine Smooth Muscle Stimulation
Bromocriptine	–	+++	–	0
Ergonovine	+	+	– (PA)	+++
Ergotamine	– (PA)	0	+ (PA)	+++
Lysergic acid diethylamide (LSD)	+/0	+++	– –/++ in CNS	+

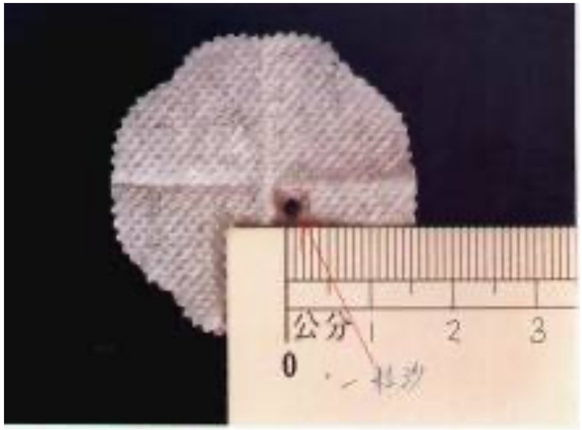
Organ System Effects The Ergot Alkaloids

- Central Nervous System
  - Lysergic acid diethylamide (LSD; "acid") is a synthetic ergot compound that clearly demonstrates this action.
  - The drug has been used in the laboratory as a potent peripheral $5\text{-}HT_2$ antagonist, but good evidence suggests that its behavioral effects are mediated by ***agonist*** effects at prejunctional or postjunctional $5\text{-}HT_2$ receptors in the central nervous system.
- Of all the currently available ergot derivatives
  - bromocriptine, **cabergoline (Dostinex®), and pergolide** have the highest selectivity for the pituitary dopamine receptors.
    - These drugs directly suppress prolactin secretion from pituitary cells by activating regulatory dopamine receptors
      - They compete for binding to these sites with dopamine itself and with other dopamine agonists such as apomorphine.

Lysergic acid diethylamide(LSD)

- History
  - 1938年亞伯特 霍夫曼(Albert Hofmann)在研究麥角生物鹼時，無意中合成了現在為大家所熟知的迷幻劑LSD；為一種麥角生物鹼衍生物
    - 0.01mg 便會產生作用
  - 別名
    - 搖腳丸、一粒砂、蟑螂屎、陽光、加州陽光…等
- 症狀
  - 心跳快、高血壓及發抖，會有情緒的起伏、時間的扭曲、視力錯覺(常看到物體或人身上鮮明的色彩會移動)、聲音會放大及扭曲、反射作用變強、無法走路、過度活動…
  - 使用LSD的病人，在戒斷不用LSD一段時間後，可能仍會有倒敘式精神異常，就如電影倒敘般，一一重新經歷以前的幻覺
- 屬於毒品危害防制條例第二級毒品





Clinical Pharmacology of Ergot Alkaloids

- Migraine
  - Ergot derivatives are highly specific for migraine pain; they are not analgesic for any other condition
    - **Ergotamine**
    - **Dihydroergotamine** (seglor®)
    - **Methysergide**
  - Noted
    - 當ergot衍生物與macrolides（例如：erythromycin）合併使用時，應小心監測是否有ergot中毒的表現（例如：周邊血管痙攣,四肢嚴重壞死）。
    - 不建議空腹使用
    - 嚴重肝機能不全和嚴重腎功能不全而未作血液透析患者，應謹慎使用。
    - 曾有動脈疾病病史者建議進行醫療監測（特別是冠狀動脈疾病和重度高血壓患者）。

cafergot®
(Ergotamine 1 mg + Caffeine 100 mg)
0
10
20
30 mm

seglor® 5mg
塞戈羅膠囊
DIHYDROERGOTAMINE MESYLATE
30
capsules
oral route
seglor® 5mg
30 capsules
Keep out of the reach of children
GlaxoSmithKline
seglor® 5mg
Only on medical prescription
Administration:
Before use, read the leaflet inside carefully.
Swallow with glass of water.

塞戈羅
seglor® 5mg
DIHYDROERGOTAMINE MESYLATE
CAPSULES/ORAL ROUTE
STRICTLY FOLLOW THE PRESCRIBED DOSES

	Sumatriptan (Imigran®)	Ergotamine/caffeine (Cafergot®)	Dihydroergotamine (Seglor®)
劑型	50 mg/tab	1/100 mg/tab	5 mg/cap
建議劑量	25-100 mg立即服用，二小時後可再服用第二劑，每次極量100 mg，每日極量300 mg	1-2顆立即服用，每30分鐘可再服用一次，每日極量六顆，每週極量十顆	1顆 bid
適應症	有先兆或無先兆偏頭痛發作之急性緩解。 本藥僅適用於有明確診斷之偏頭痛	血管性頭痛、偏頭痛	偏頭痛

- Hyperprolactinemia
  - **Bromocriptine** →D_2 agonist→prolactin ⬇
    - The usual dosage of bromocriptine is 2.5 mg two or three times daily.
    - **Cabergoline** is similar but more potent.

- Postpartum Hemorrhage (產後出血)
  - ergot derivatives should be used only for control of late uterine bleeding and should never be given before delivery.
  - **Oxytocin** is the preferred agent for control of postpartum hemorrhage, but if this peptide agent is ineffective, ergonovine maleate, 0.2 mg given intramuscularly, can be tried.

Toxicity & Contraindications

- The most common toxic effects of the ergot derivatives are
  - **gastrointestinal disturbances**, including diarrhea, nausea, and vomiting.
- A more dangerous toxic effect of overdosage with agents like ergotamine and ergonovine is prolonged vasospasm.
- Chronic therapy with methysergide was associated with
  - connective tissue proliferation in the retroperitoneal space, the pleural cavity, and the endocardial tissue of the heart.
    - 腹膜後纖維化，心肌纖維化，胸膜纖維化
- Drowsiness

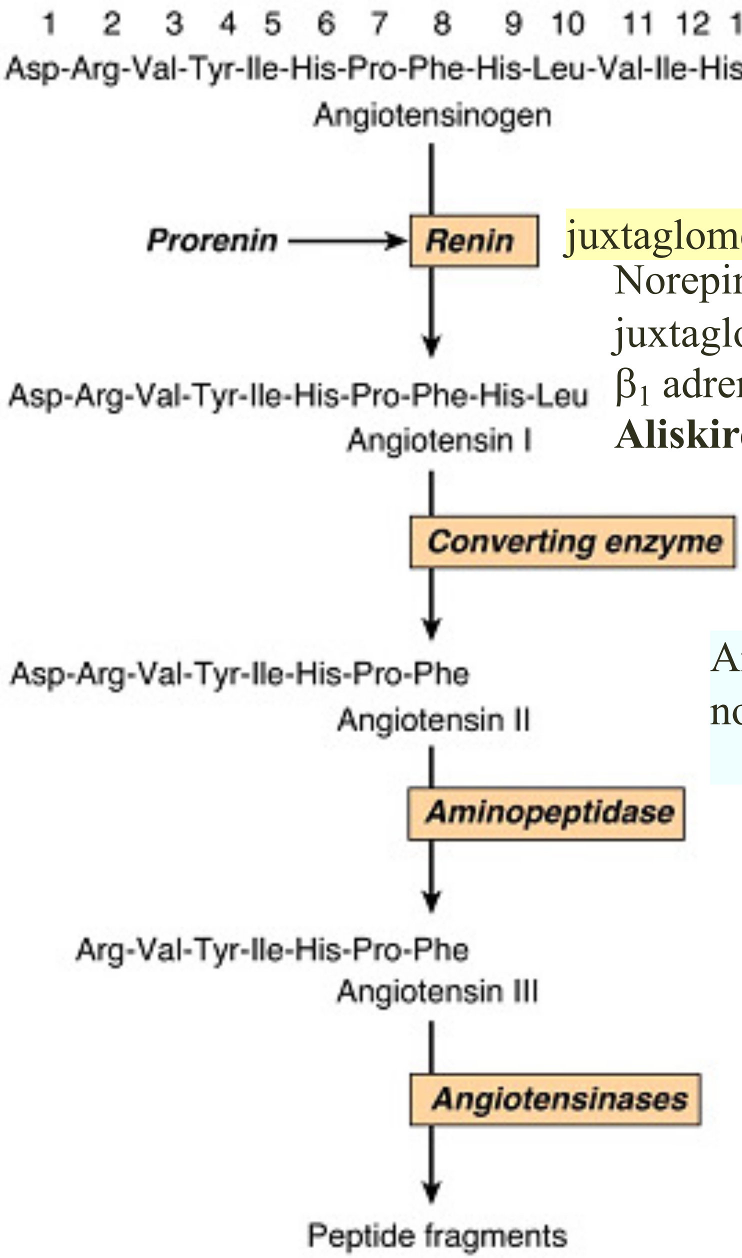
Chapter 17

Vasoactive Peptides

Vasoactive Peptides

- These peptides include
  - Vasoconstrictors
    - angiotensin II
    - Vasopressin
    - Endothelins
    - neuropeptide Y
    - urotensin
  - Vasodilators
    - Bradykinin
    - related kinins
    - natriuretic peptides
    - vasoactive intestinal peptide
    - substance P
    - Neurotensin
    - calcitonin gene-related peptide
    - adrenomedullin)

Angiotensin



juxtaglomerular cells: are the site of synthesis, storage, and release of renin.

Norepinephrine stimulates renin secretion by a direct action on the juxtaglomerular cells. In humans, this effect is mediated by β_1 adrenoceptors.

Aliskiren: suppresses plasma renin activity

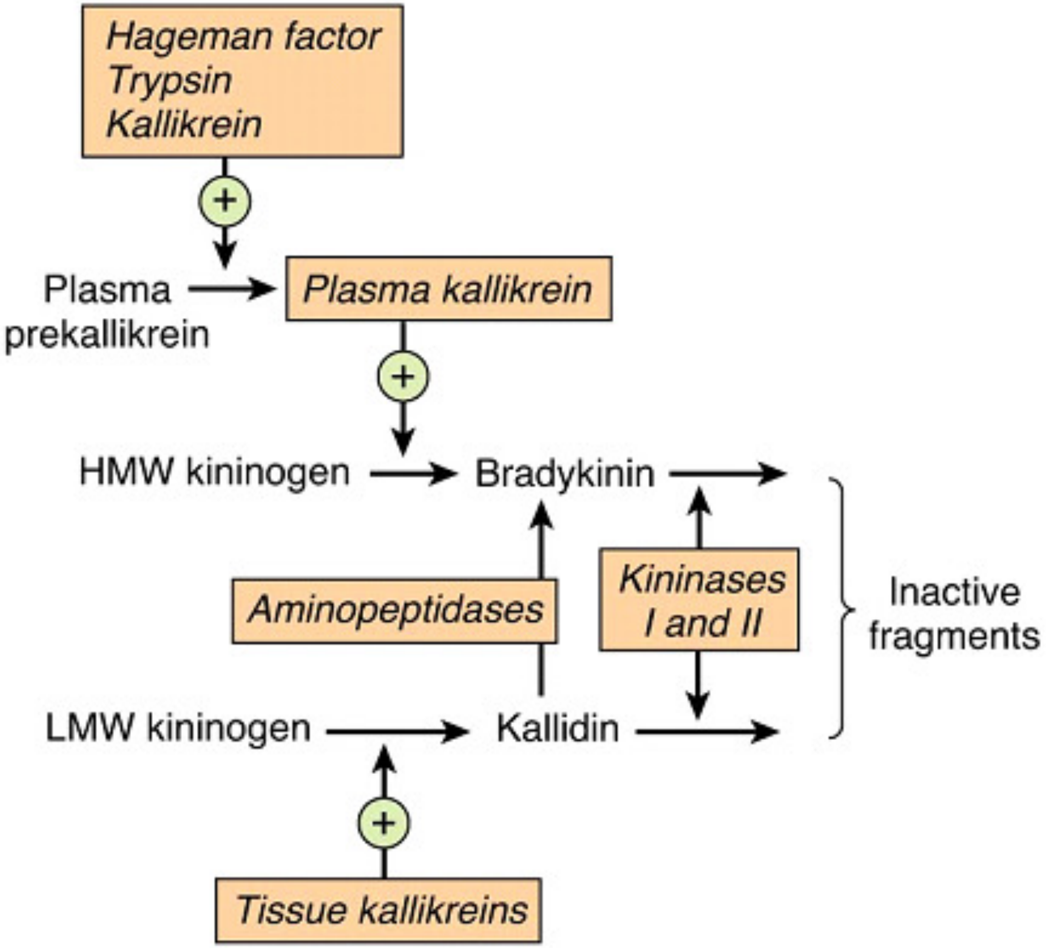
Captopril and enalapril

Ang II receptor blockers (ARBs): saralasin (peptide).

non peptide ARBs: Losartan, valsartan, eprosartan, irbesartan, **candesartan**, olmesartan, and telmisartan

Kinins

- Kinins: potent vasodilator peptides
  - Three kinins have been identified in mammals
    - Bradykinin
    - lysylbradykinin (also known as kallidin)
    - methionyllysylbradykinin



Physiologic & Pathologic Effects of Kinins

- Effects on the Cardiovascular System
- Effects on Endocrine & Exocrine Glands
- Role in Inflammation
- Effects on Sensory Nerves
- Other Effects
  - bradykinin may play a beneficial, protective role in certain cardiovascular diseases and ischemic stroke-induced brain injury

Kinin Receptors & Mechanisms of Action

- Two types of kinin receptors, **termed B_1 and B_2**, have been defined based on the rank orders of agonist potencies.
  - Note that *B* here stands for bradykinin, not for β-adrenoceptor
    - B_1 receptors
      - appear to have a very limited distribution in mammalian tissues and have few known functional roles.
    - B_2 receptors
      - are G protein–coupled and agonist binding sets in motion multiple signal transduction events, including calcium mobilization, chloride transport, formation of nitric oxide, and activation of phospholipase C, phospholipase A_2, and adenylyl cyclase.

Icatibant

- Mechanism
  - B_2 receptor antagonist.
- Actions
  - Icatibant has been used extensively in animal studies to block exogenous and endogenous bradykinin and in human studies to evaluate the role of kinins in pain, hyperalgesia (高敏感度疼痛) , and inflammation.
- Indications
  - It shows promise for use in the treatment of hereditary angioedema and pain.

Vasopressin

- Vasopressin (**antidiuretic hormone, ADH**)
  - plays an important role in the long-term control of blood pressure through its action on the kidney to increase water reabsorption.
- Three subtypes of vasopressin receptors
  - **V_1 receptors**
    - **V_{1a} receptors** mediate the vasoconstrictor action of vasopressin
    - **V_{1b} receptors** potentiate the release of ACTH by pituitary corticotropes
  - **V_2 receptors** mediate the antidiuretic action

Terlipressin

- Mechanism
  - V_1 receptor agonist
- Actions
  - A synthetic vasopressin analog that is converted to lysine vasopressin in the body
  - It may have advantages over vasopressin because it is more selective for V1 receptors and has a longer half-life
- Indications
  - Bleeding esophageal varices (食管靜脈曲張)
  - 第一型肝腎症候群
- Side effects
  - Abdominal cramps; headache; transient blanching; increase in arterial BP

- Conivaptan
  - Mechanism
    - V_1 receptor antagonist
  - Actions
    - Vasodilation
  - Indications
    - Potential use in hypertension and heart failure hyponatremia (低鈉血症)
  - Side effects
    - hypotension

Natriuretic Peptides

- The atria and other tissues of mammals contain a family of peptides with natriuretic, diuretic, vasorelaxant, and other properties
  - The family includes
    - Atrial natriuretic peptide (ANP)
    - Brain natriuretic peptide (BNP)
      - **nesiritide**
    - C-type natriuretic peptide (CNP).

Nesiritide

- Mechanism
  - BNP receptor agonist
- Actions
  - Increased sodium and water excretion
  - vasodilation
- Indications
  - Heart failure
- Side effects
  - Renal damage
  - hypotension

Endothelins

- The endothelium is the source of a variety of substances with vasodilator (PGI_2 and nitric oxide) and vasoconstrictor activities.
  - Structure
    - **ET-1**
      - central nervous system, renal mesangial..
    - **ET-2**
      - kidneys and intestine
    - **ET-3**
      - brain
  - Receptors
    - **ET_A** Receptor
      - vasoconstriction
    - **ET_B** Receptor
      - release of PGI2 and nitric oxide

Bosentan

- Mechanism
  - ET_A and ET_B receptor antagonist
- Actions
  - Vasodilation
- Indications
  - Pulmonary hypertension
- Side effects
  - Hepatic impairment; possible teratogen (致畸胎)

Substance P

- tachykinin family of peptides
  - Substance P (the most important)
    - In the central nervous system
    - In the gastrointestinal tract
  - Neurokinin A
  - Neurokinin B

mediated by **NK_1** , **NK_2** , and **NK_3** receptor → **behavior, anxiety, depression, nausea, emesis, potent vasodilator…**

Aprepitant (Emend®)

- Mechanism
  - Tachykinin NK_1 receptor antagonist
- Actions
  - Blocks several central nervous system effects of substance P
- Indications
  - Antiemetic for chemotherapy-induced vomiting
- Side effects
  - Asthenia, hiccups

    (無力，打嗝)

EMEND®
(aprepitant, MSD)
80 mg
1 Capsule
MSD
止敏吐®
膠囊 80 公絲
本藥須由醫師處方使用
衛署藥輸字第 023985 號
製造廠：Merck & Co., Inc.美國默克藥廠
藥　商：美商默沙東藥廠股份有限公司
台灣分公司
地　址：台北市敦化南路二段216號14樓
Each capsule contains 80 mg aprepitant.
For Dosage and Administration, Contraindications, Precautions/Warnings, see accompanying circular.
Keep medicines out of the reach of children.
Store at or below 30°C.
Manufactured by:
MERCK & CO., Inc.
770 Sumneytown Pike, West Point, Pennsylvania, 19486 USA
Packed by:
Merck Sharp & Dohme (Australia) Pty. Limited
54-68 Ferndell Street, South Granville, N.S.W. 2142, Australia

EMEND®
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80 mg
MSD
LOT N3722
EXP 02.2013

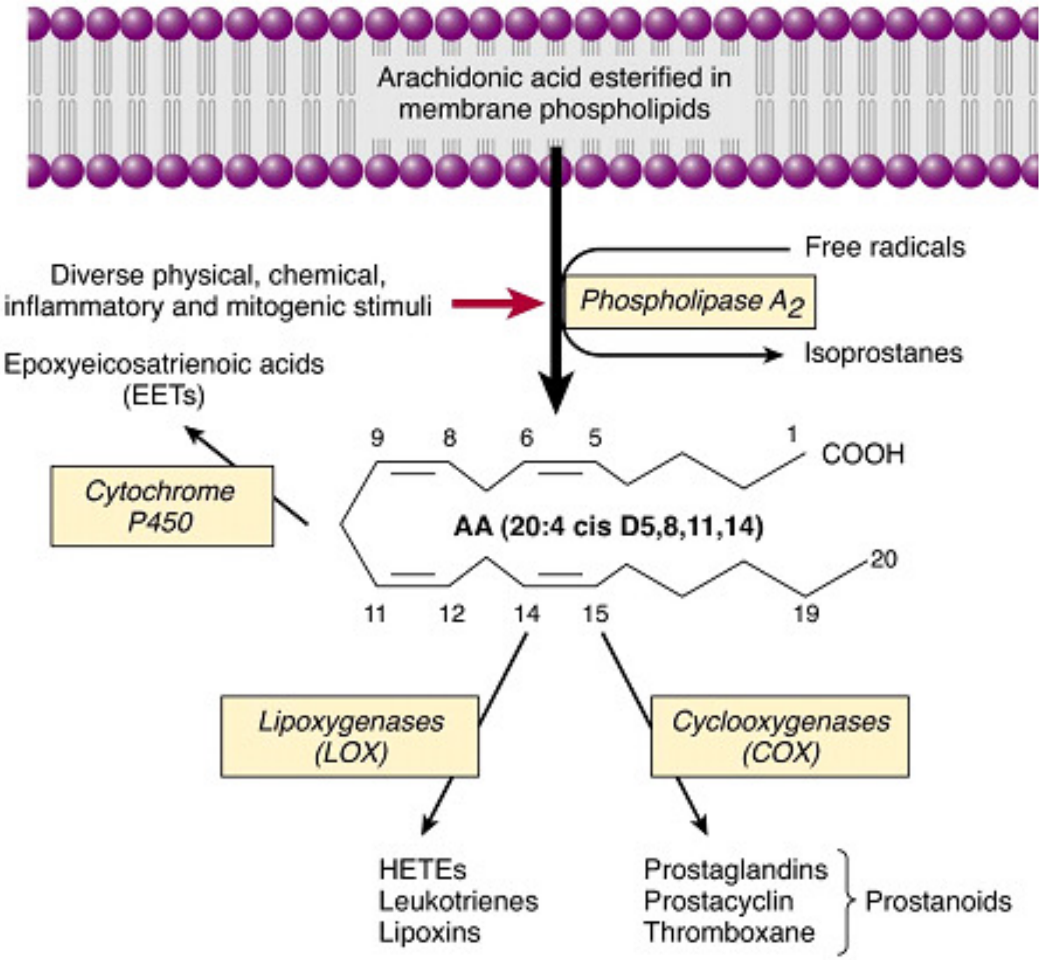
461
80 mg
1
2
3
4

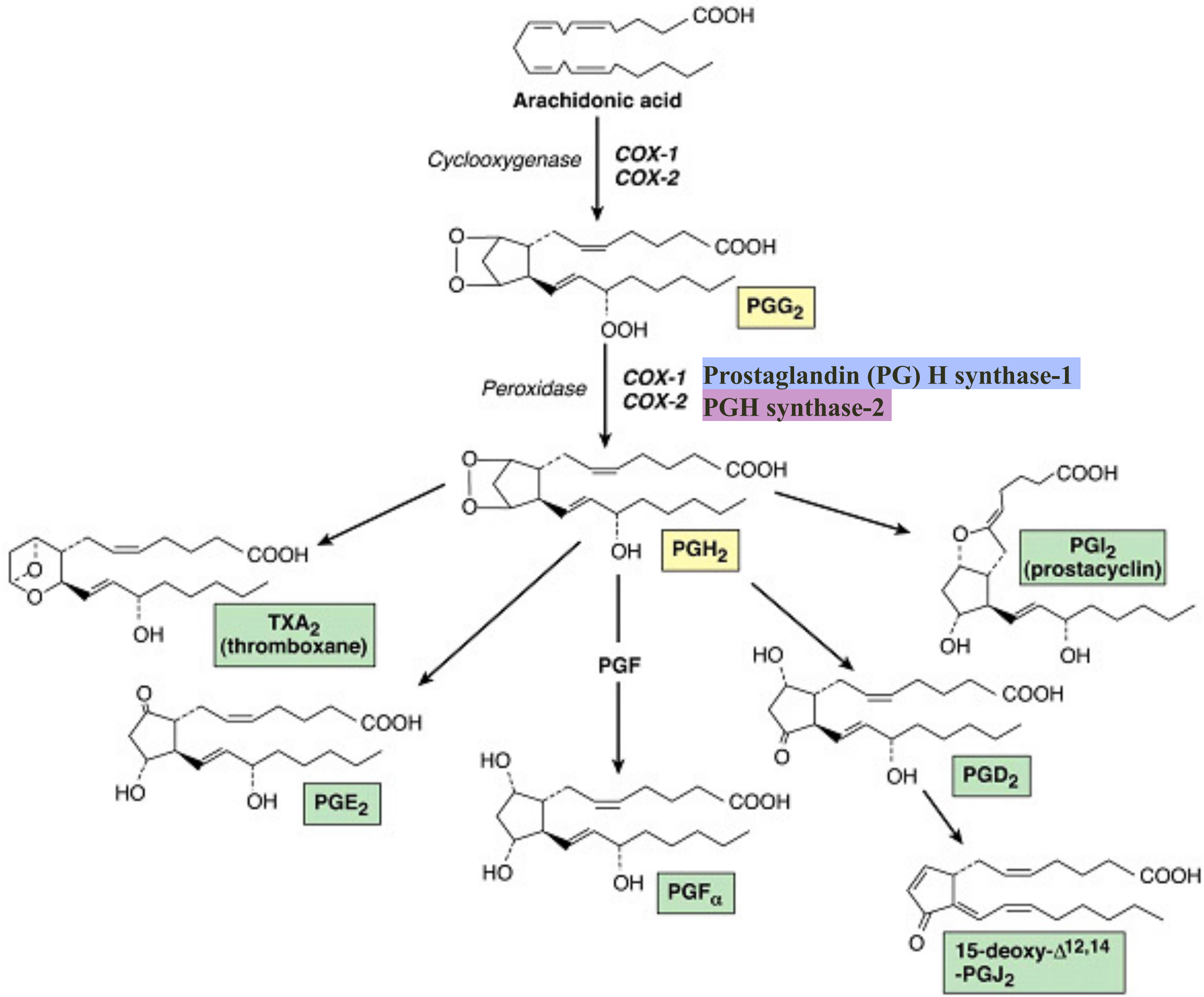
Chapter 18

The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds

The Eicosanoids

- The eicosanoids are oxygenation products of polyunsaturated long-chain fatty acids
  - plants
  - Animals (fish)
- AA is oxygenated by four separate routes
  - cyclooxygenase (COX)
  - Lipoxygenase
  - P450 epoxygenase
  - isoeicosanoid pathways





COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
PGG2
OOH
Peroxidase
COX-1
COX-2
Prostaglandin (PG) H synthase-1
PGH synthase-2
COOH
OH
PGH2
COOH
OH
TXA2
(thromboxane)
COOH
PGI2
(prostacyclin)
OH
OH
PGF
COOH
HO
OH
PGE2
HO
COOH
HO
OH
PGFα
HO
COOH
OH
PGD2
COOH
15-deoxy-Δ12,14
-PGJ2

Cyclooxygenase

- Activity of inhibition
  - Indomethacin and sulindac
    - COX-1 > COX-2
  - Meclofenamate, ibuprofen and Aspirin
    - COX-1 = COX-2
- Inhibition of COX-2
  - celecoxib = diclofenac < rofecoxib = lumiracoxib < etoricoxib

Summary

	Aspirin	Ibuprofen	Naproxen	Voltaren	Ponstan	Piroxicam	Indome-thacin	Sulindac
類風濕性關節炎	√	√	√	√		√	√	√
骨關節炎	√	√	√	√		√	√	√
關節硬化性脊椎炎	√		√	√			√	√
肌腱炎	√		√				√	√
黏液囊炎	√		√				√	√
急性肩痛	√	√	√				√	√
急性痛風	√		√				√	√
原發性經痛	√			√	√			
輕度至中度的疼痛	√	√			√			
發燒	√							

NSAIDs副作用

藥 名	鎮痛	抗發炎	半衰期	主要副作用
Aspirin	++	+++	5-10	腸胃刺激, 耳鳴
Panadol	++		3-5	肝毒性
Indomethacin	++	++++	2-5	腸胃刺激, 頭痛, 痙攣
Sulindac	++	+++	16	腸胃刺激, 頭暈,
Ibuprofen	++	++	3-4	皮膚癢, 頭痛
Naproxen	++	+++	13	皮膚癢, 腸胃刺激,
Diclofenac	++	+++	3-5	腸胃刺激, 頭暈,
Mefenamate	++	+	2-3	下痢, 溶血性貧血
Piroxicam	++	+++	38-45	腸胃刺激, 皮膚癢, 水腫

NSAIDs副作用

Drug	出血傾向	潰瘍	下痢	意識障礙	腎毒性	引發氣喘
Aspirin	++++	+++	±	++	+	++
Ibuprofen	++	++	+	+	+	++
Fenoprofen	++	++	+	+	+	++
Naproxen	++	++	+	+	+	++
Sulindac	++	++	++	+	±	++
Piroxicam	++	++	+	+	+	++

NSAIDs 不良反應出現的百分比

Drug	腸胃刺激	腎臟毒性	中樞毒性	皮膚癢	肝毒性	過敏	血液毒性
Aspirin	25-70	18-39	10	< 1	< 5	< 1	20-60
Ibuprofen	8-27	3-10	3-9	3-9	< 1	< 1	< 1
Naproxen	10-32	3-9	3-9	3-9	< 1	< 1	< 1
Indomethacin	15-45	< 1	10-50	< 1	< 1	< 1	< 1
Sulindac	10-21	< 1	3-9	3-9	< 1	< 1	< 1
Piroxicam	15-30	< 3	< 3	< 3	< 1	< 1	< 1

	腸胃刺激	潰瘍	中樞神經	耳鳴	肝炎	腎障礙
Mefenamic acid	+	+	+	-	-	++
Indomethacin	++++	+++	+++	+	+	++
Sulindac	+	+	+	+	+	+
Piroxicam	+++	+++	+	+	+	+
Diclofenac	++	++	+	+	++	+
Ibuprofen	++	+	+	+	+	+
Naproxen	+	++	++	++	+	+
Aspirin	++++	++	+	+++	++	+

老年人使用NSAIDs之原則

- 以一般成人劑量之半量開始
- 有胃腸不適者可用Sulindac或是COX-2抑制劑
- 有腎功能不全者可用Sulindac
- 建議使用
  - Ibuprofen, Acetaminophene, COX-2抑制劑
- 避免使用
  - Aspirin, Indomethacin, Piroxicam

老年病患治療輕中度疼痛的方法

- 先使用Acetaminophen 500-100mg (最大劑量 4000mg/天)按時給藥(隔六小時)至疼痛改善 但注意肝毒性的監測
- 若疼痛持續 則改用非類固醇消炎鎮痛藥 如 Ibuprofen, Ketoprofen注意血壓 腎功能及腸胃刺激的監測
- 若疼痛持續 則改用另一類之非類固醇消炎鎮痛藥 如 Sulindac, COX-2抑制劑
- 亦可於短期中使用Acetaminophen 加一種非類固醇消炎鎮痛藥，但避免同時使用兩種非類固醇消炎鎮痛藥

孕婦及哺乳婦女使用NSAIDs注意事項

- NSAIDs對孕婦之影響
  - 懷孕時間延長
  - 產期延長
  - 生產前後出血量增加
  - 貧血
  - 子癇前症及妊娠毒血症
- NSAIDs對胎兒的影響
  - 凝血機能異常
  - 顱內出血之意外增加
  - 動脈導管早期閉鎖
  - 持續性肺高血壓

藥物	孕婦用藥分級
Aspirin	D
Diclofenac	B/D
Ibuprofen	B/D
Indomethacin	D
Mefenamic acid	C
Naproxen	B
Sulindac	B/D
Acetaminophen	B

孕婦使用NSAIDS之原則

- NSAID在懷孕最後三各月不可長期使用
  - 因為會抑制 Prostaglandin 之合成，而導致延長母親懷孕與生產時間，並影響胎兒出生後之血液肺循環
- Diclofenac, Ibuprofen, Napoxen, Sulindac
  - 孕婦必要時可以服用，但在生產前三個月間則不可長期服用。
- Acetaminophen為懷孕期間較安全之鎮痛藥
- 避免使用毒性較大或作用時間太長NSAID
  - Piroxicam, Indomethacin, Mefenamic acid,

NSAIDs病患用藥注意事項(1)

病患狀況	推薦使用或避免服用的藥物
氣 喘	避免使用Aspirin 可用 Diclofenac
消化性潰瘍	小心服用 或使用 H_2-antagonist or misoprostol 預防
肝病	避免Diclofenac 及 Acetaminophene
腎臟疾病	使用Sulindac 或nonacetylated salicylate
高血壓	使用Sulindac 避免indomethacin
老年人	使用半衰期較短者
痛風 急性炎症	服用Indomethacin
外科手術	開刀前一星期 停用Aspirin, Piroxicam 前一天停用全部的解熱鎮痛劑

NSAIDs病患用藥注意事項(2)

1. 兩種不同之NSAID併用時,鎮痛作用無法相加,但副作用常相乘。
2. 避免長期或過量使用NSAID
3. 飯後服藥或併用制酸劑 可減低腸胃障礙 肛門栓劑亦較無腸胃刺激性
4. 服藥時 若出現皮膚癢 紅疹 光敏感性時 請停藥
5. 服藥時 若同時飲酒 會增加腸胃及中樞神經的不良反應
6. 忘記服藥時 應儘快補服但與下一劑量時間很接近時請勿補服或加大劑量
7. 減低腸胃刺激性的方法
   - 用於止痛時儘量用低劑量
   - 以約 200ml開水併服
   - 不要躺著服藥
   - 戒煙 避免含酒精的飲料
   - 吃飯時與食物併服
   - 使用較無腸胃刺激者 如Acetaminophen, Sulindac, COX-2抑制劑等
   - 使用 H2-antagonist, sucralfate 或 misoprostol 預防

Effects of Prostaglandins & Thromboxanes

- Smooth Muscle
  - Vascular
  - Gastrointestinal Tract
  - Airways
  - Reproductive
- Platelets
- Kidney
- Reproductive Organs
  - Female Reproductive Organs
  - Male Reproductive Organs
- Central and Peripheral Nervous Systems
  - Fever
  - Sleep
  - Neurotransmission
- Inflammation and Immunity
- Bone Metabolism
- Eye
- Cancer

Effects of Lipoxygenase & Cytochrome P450-Derived Metabolites

- Blood Cells and Inflammation
- Heart and Smooth Muscle
  - Cardiovascular
  - Gastrointestinal
  - Airways
- Renal System
- Miscellaneous

Effects of eicosanoids
(Prostaglandins & Thromboxanes & Leukotrienes)

Effect	PGE_2	$PGF_{2\alpha}$	PGI_2	TXA_2	LTB_4	LTC_4	LTD_4
Major receptors	EP_{1-4}	$FP_{A,B}$	IP	TP	$BLT_{1,2}$	$CysLT_2$	$CysLT_1$
Vascular tone	↓	↑or↓	↓↓	↑↑↑	?	↑or↓	↑or↓
Bronchial tone	↓↓	↑↑	↓	↑↑↑	?	↑↑↑↑	↑↑↑↑
Uterine tone	$↑_{low}$,↓	↑↑↑	↓	↑↑	?	?	?
Platelet aggregation	or		↓↓↓	↑↑↑	?	?	?
Leukocyte chemotaxis	?	?	?	?	↑↑↑↑	↑↑	↑↑

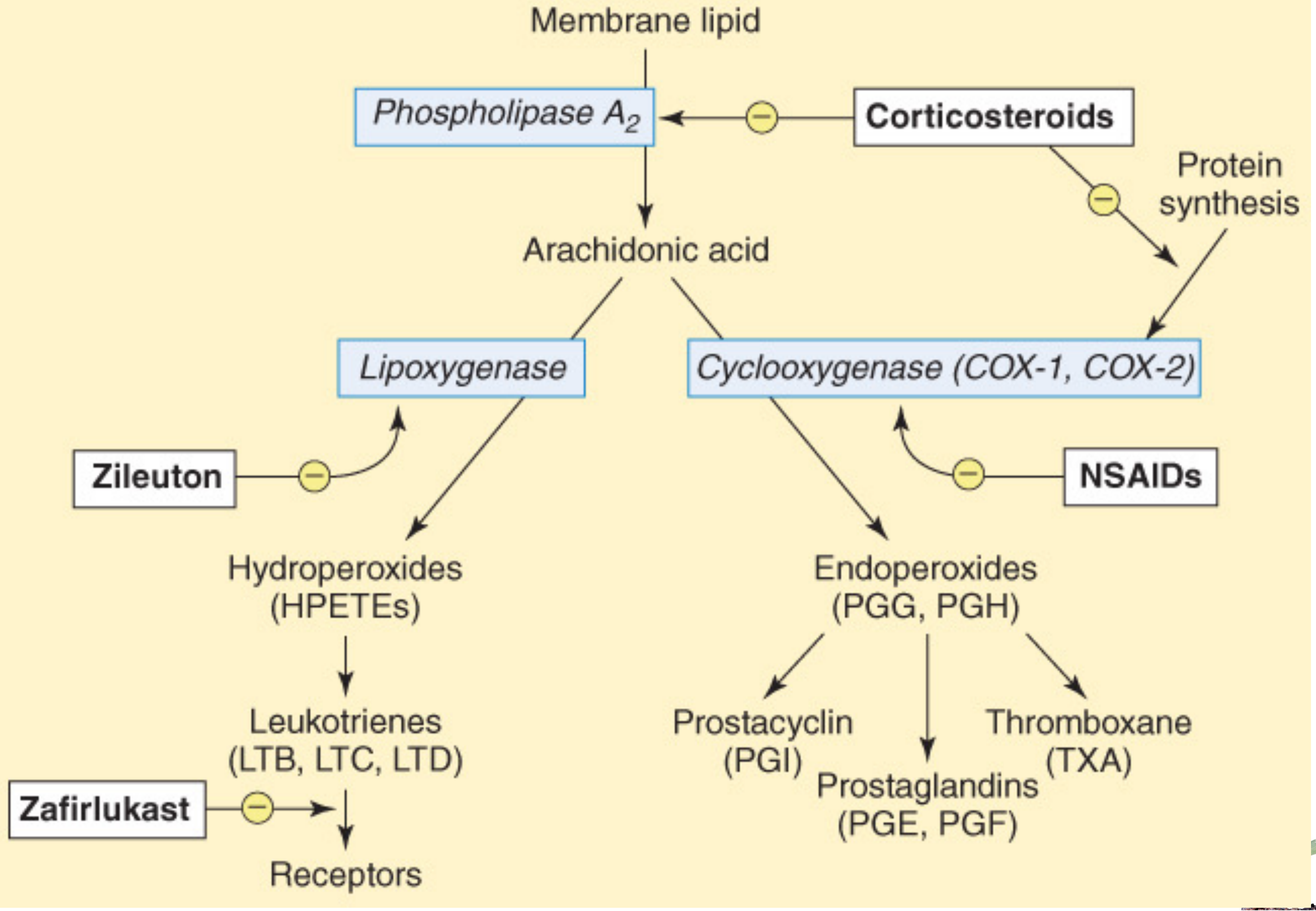
PGE_2 receptors (EPs 1–4)
$PGF_{2\alpha}$ receptor (FP)
PGI2 receptor (IP)
TXA_2 receptor (TP)
PGD_2 receptors (DP_1 and DP_2)

LTB4 receptors (BLT1 and BLT2)
cysteinyl leukotrienes (cysLT1 and cysLT2).

前列腺素之生理作用

作用	前列腺素
血管擴張 血管收縮	PGD_2 PGE_2 PGI_2 $PGF_{2\alpha}$ TXA_2
支氣管擴張 支氣管收縮	PGE_2 PGI_2 PGD_2 $PGF_{2\alpha}$ TXA_2
促進血小板凝集 抑制血小板凝集	TXA_2 PGD_2 PGI_2
子宮擴張 子宮收縮	PGE_2 PGI_2 PGE_2 $PGF_{2\alpha}$

Inhibition of Eicosanoid Synthesis



Clinical Pharmacology of Eicosanoids

- Abortion (人工流產)
  - PGE_2 and $PGF_{2\alpha}$
    - have potent oxytocic actions. The ability of the E and F prostaglandins and their analogs to terminate pregnancy at any stage by promoting uterine contractions has been adapted to common clinical use.
  - Dinoprostone
    - a synthetic preparation of PGE_2
      - Antiprogestins (eg, **mifepristone**) have been combined with an oral oxytocic synthetic analog of PGE1 (**misoprostol**) to produce early abortion
      - Side effects
        - Cramping, fetal trauma (抽筋，胎兒創傷)
  - Carboprost
      - An analog of $PGF_{2\alpha}$ is also used in obstetrics (產科學)

Mifepristone (RU486)

- 使用方法:
  - 確認懷孕(且一定要是子宮內孕)
  - 使用時機需距上次月經之第一天的49天內，需在診間醫護人員面前服藥,且須簽署同意書
  - 服完RU486, 36-48小時後服用Misoprostol (cytotec®)誘發子宮收縮，服藥後3小時內需留在醫療院所觀察
  - 病患需於2週內回診,確認完全流產

Mifepristone(RU486)

- 注意事項
  - 流產出血天數約12天，如超過兩星期,便需再做子宮清除術
  - 在兩個月內應有正常月經發生
  - 且因如此高劑量的藥物刺激,可能對胎兒造成先天的傷害，懷孕級數：X級
  - 嚴禁用在子宮外孕、氣喘、心血管疾病、35歲以上有抽煙習慣者

Male Reproductive System

- **alprostadil** (PGE$_1$)
  - Mechanism of Action
    - Relaxes smooth muscle in ductus arteriosus
  - Indications
    - Transposition of great vessels, to maintain patent ductus until surgery
      - 新生兒先天性心臟缺損之緩解
    - is a second-line treatment for erectile dysfunction
  - Side effects
    - Hypotension
    - Penile pain

- Pulmonary Hypertension
  - epoprostenol (PGI_2)
    - Mechanism of Action
      - Activates IP receptors, causes vasodilation, reduces platelet aggregation
    - Indications
      - Vasodilator in pulmonary hypertension, antiplatelet agent in extracorporeal dialysis (體外透析)
    - Side effects
      - Hypotension, flushing, headache
  - Analogue
    - Iloprost
      - inhaled six to nine times per day
    - Treprostinil

Respiratory System

A. leukotriene -receptor inhibitors (eg, zafirlukast, montelukast (Singulair®)

- Mechanism of Action
  - Block $CysLT_1$ receptor; reduce bronchoconstriction in asthma
- Indications
  - Asthma prophylaxis
- Side effects
  - GI disturbances, headache, Liver enzyme elevation…
- Note
  - Should be taken on an empty stomach. (Take at least 1 hr before or 2 hr after meals.)

MSD
SINGULAIR®
montelukast sodium
MSD
10 mg Tablets
SINGULAIR®
montelukast sodium
SINGULAIR
4 mg
MSD

THUR
SINGULAIR®
tablets 10 mg
欣流® 膜衣錠 10公絲
FRI
WED
SINGULAIR®
tablets 10 mg
欣流® 膜衣錠 10公絲
SAT
MSD 美商默沙東藥廠
股份有限公司台灣分公司
衛署藥輸字第022778號
TUES
SINGULAIR®
tablets 10 mg
欣流® 膜衣錠 10公絲
SUN
MON
SINGULAIR®
tablets 10 mg
欣流® 膜衣錠 10公絲
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B. lipoxygenase inhibitor (zileuton)

- Mechanism of Action
  - Blocks synthesis of leukotrienes
- Indications
  - Asthma prophylaxis
- Side effects
  - Liver enzyme elevation

- Gastrointestinal System
  - Misoprostol (Cytotec®)is an orally active synthetic analog of PGE_1
    - Mechanism of Action
      - Activates EP receptors, causes increased HCO^{3-} and mucus secretion in stomach; uterine contraction
    - Indications
      - Protective agent in peptic ulcer disease
        - » FDA-approved indication is for prevention of NSAID-induced peptic ulcers
      - Abortifacient (墮胎)
    - Side effects
    - Diarrhea, uterine cramping

- Glaucoma
  - Latanoprost, a stable long-acting $PGF_{2\alpha}$ derivative
    - Mechanism of Action
      - Increases outflow of aqueous humor, reduces intraocular pressure
    - Indications
      - Glaucoma
    - Side effects
      - Color change in iris

Dietary Manipulation of Arachidonic Acid Metabolism

- ω-3 fatty acid (n-3 fatty acid)
  - **Alpha-linolenic acid (ALA), EPA and DHA**
    - eicosapentaenoic (C20:5) and docosahexaenoic acids (C22:6),
- ω-6 fatty acid (n-6 fatty acid)
  - **linoleic acid (=Linolic acid)**
    - safflower, and sunflower oils, which contain linoleic acid (C18:2)
  - **Gamma-linolenic acid (GLA)**
  - **Arachidonic acid**

Omega-6 Pathway

Common in healthy diet

Linoleic acid (18:2)

↓ desaturation

γ-Linolenic acid (18:3)

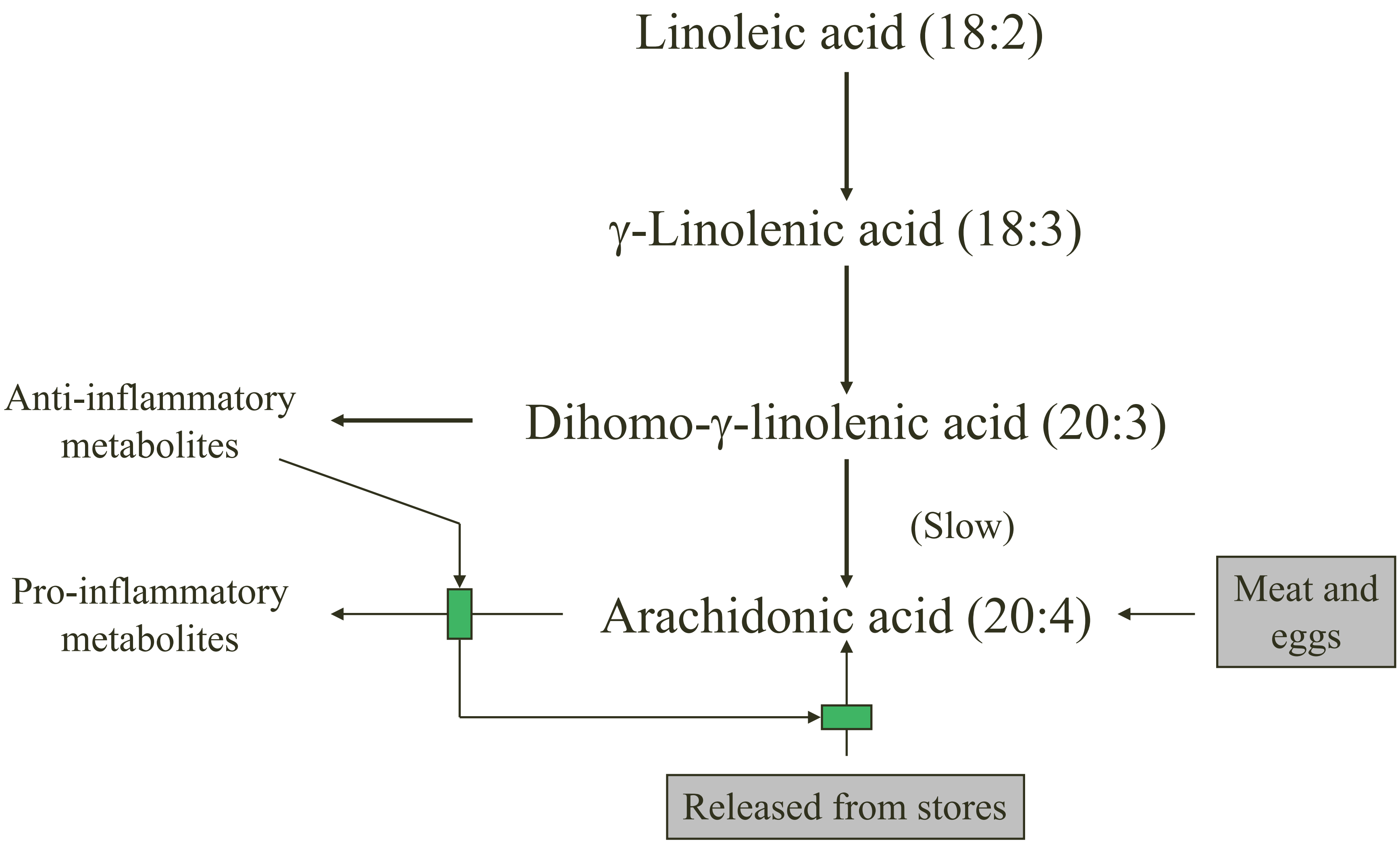
↓ elongation

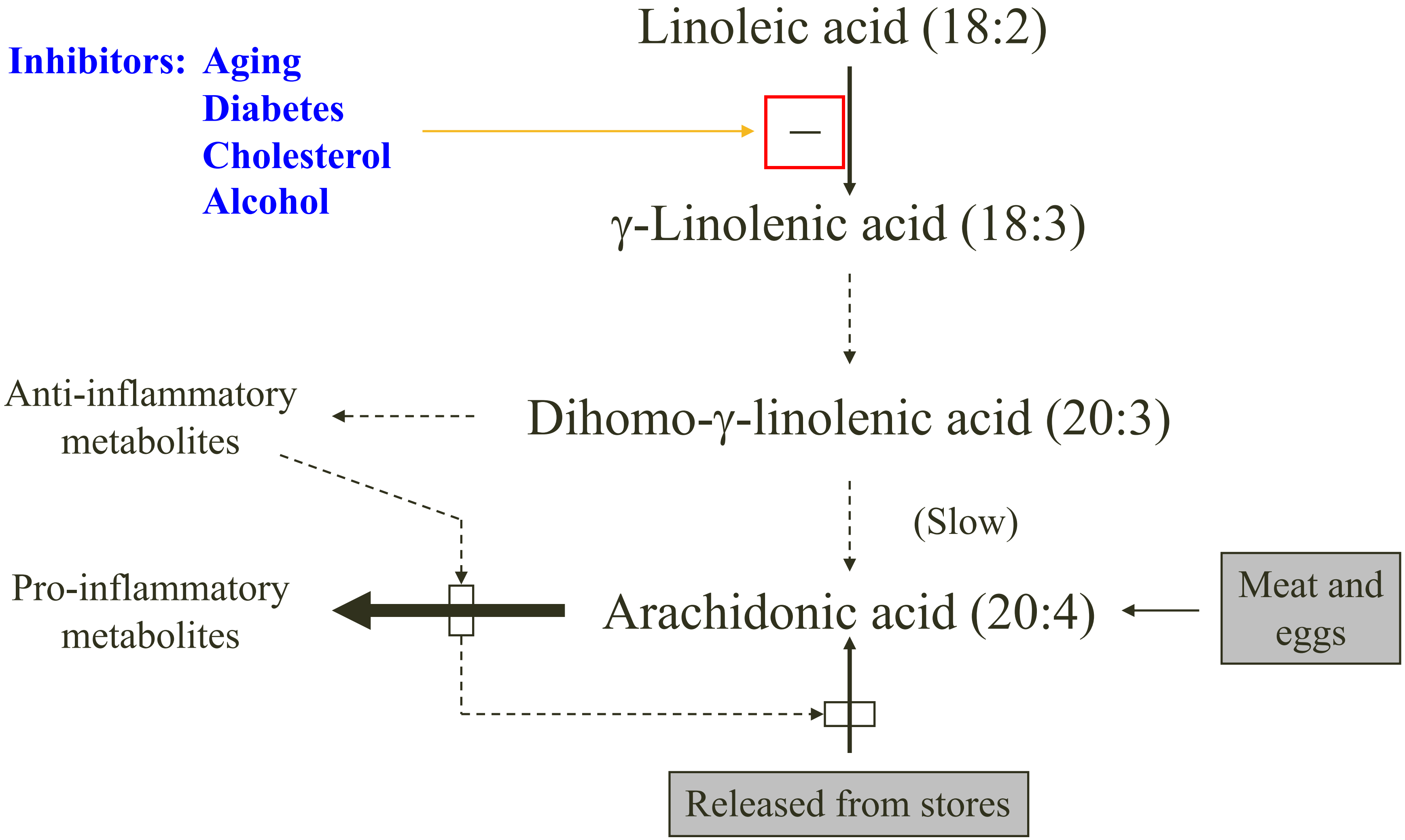
Dihomo-γ-linolenic acid (20:3)

↓ desaturation

Arachidonic acid (20:4)

Some available from meat and eggs


Linoleic acid (18:2)
γ-Linolenic acid (18:3)
Anti-inflammatory metabolites
Dihomo-γ-linolenic acid (20:3)
(Slow)
Pro-inflammatory metabolites
Arachidonic acid (20:4)
Meat and eggs
Released from stores


Inhibitors: Aging
Diabetes
Cholesterol
Alcohol
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–
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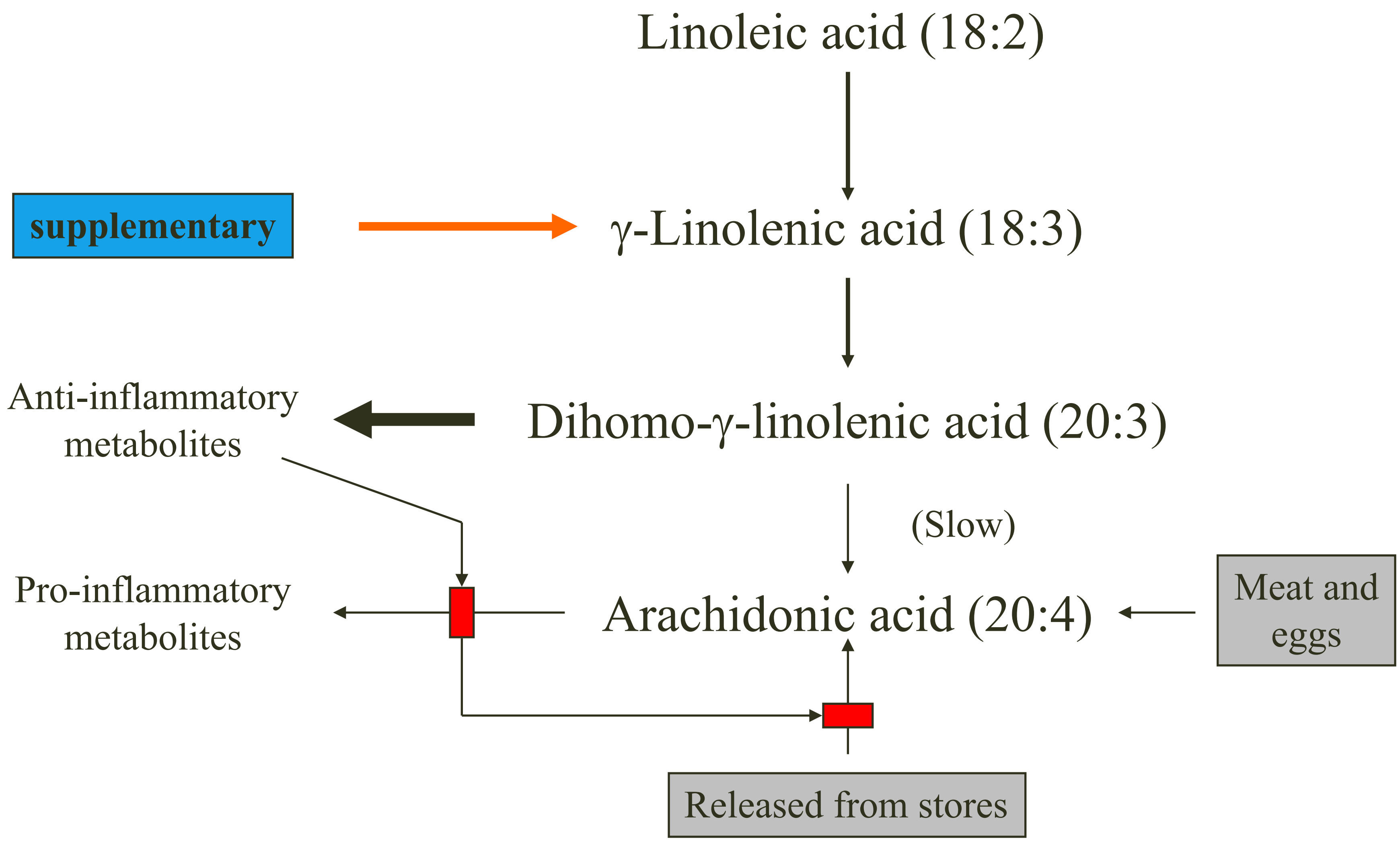
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(Slow)
Pro-inflammatory metabolites
Arachidonic acid (20:4)
Meat and eggs
Released from stores

Thank You !